IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

WILSON et al — Atty. Ref.: 3911-21

Serial No. Unassigned — TC/A.U.: Unassigned

Filed: January 30, 2004 — Examiner: Unassigned

For: BENZOAZINE MONO-N-OXIDES AND BENZOAZINE 1,4 DI-N-OXIDES AND COMPOSITIONS THEREFROM FOR THE THERAPEUTIC USE IN CANCER TREATMENTS

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January 30, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

SUBMISSION OF PRIORITY DOCUMENTS

It is respectfully requested that this application be given the benefit of the foreign filing date under the provisions of 35 U.S.C. §119 of the following, a certified copy of which is submitted herewith:

Application No.	Country of Origin	Filed
NZ 524770	New Zealand	14 March 2003

Respectfully submitted,

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Ministry of Economic Development
Manatū Ōhanga
Intellectual Property Office of New Zealand

CERTIFICATE

This certificate is issued in support of an application for Patent registration in a country outside New Zealand pursuant to the Patents Act 1953 and the Regulations thereunder.

I hereby certify that annexed is a true copy of the Provisional Specification as filed on 14 March 2003 with an application for Letters Patent number 524770 made by Auckland UniServices Limited.

Dated 23 January 2004.

Neville Harris
Commissioner of Patents, Trade Marks and Designs

COMMISSIONER OF PATENTS, TRADEMARKS & DESIGNS
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524770

Patents Form No. 4

Our Ref: JC218627

Patents Act 1953
PROVISIONAL SPECIFICATION

BENZOAZINE MONO-N-OXIDES AND BENZOAZINE 1,4 DI-N-OXIDES AND COMPOSITIONS THEREFROM FOR THE THERAPEUTIC USE IN CANCER TREATMENTS

We, **Auckland UniServices Limited**, a New Zealand company, of Level 10, 70 Symonds Street, Auckland, New Zealand do hereby declare this invention to be described in the following statement:

PT0499774

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BENZOAZINE MONO-N-OXIDES AND BENZOAZINE 1,4 DIOXIDES AND COMPOSITIONS THEREFROM FOR THE THERAPEUTIC USE IN CANCER TREATMENTS

TECHNICAL FIELD

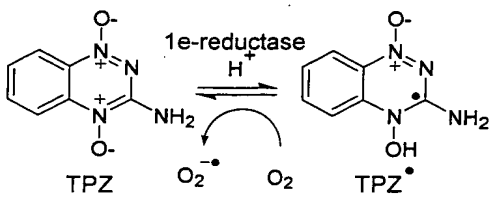
The present invention relates generally to a cytotoxic synergistic composition comprising one or more benzoazine-mono-N-oxides, and an effective amount of one or more benzoazine 1,4 dioxides for use as anticancer drugs and as radiosensitizers for cancer therapy in combination with radiation and/or other anticancer drugs.

The present invention also relates to the provision of a range of novel 1,2,4-benzoazine-mono-N-oxides and related analogues, and to their use as potentiators of the cytotoxicity of anticancer drugs and as radiosensitizers for cancer therapy in combination with radiation and/or with other anticancer agents, or to at least provide the public with a useful choice.

The term benzoazine used throughout this specification is to be understood as a term used to encompass the mono and di N- oxide derivatives of benzotriazines and quinoxalines.

BACKGROUND TO THE INVENTION

Hypoxic cells in tumours are resistant to ionising radiation, and are a major cause of treatment failure in radiation therapy (Movsas et al., *Cancer*, **2000**, 89, 2018; Rudat et al., *Radiother. Oncol.*, **2000**, 57, 31). Hypoxic cells are also considered to compromise response of solid tumours to cytotoxic chemotherapy (Brown and Giaccia, *Cancer Res.*, **1998**, 58, 1408). The benzotriazine di-N-oxide tirapazamine (TPZ) is selectively toxic to hypoxic cells because of its metabolic activation to a cytotoxic species by one-electron reduction (Baker et al., *Cancer Res.*, **1988**, 48, 5947; Laderoute et al., *Biochem. Pharmacol.*, **1988**, 37, 1487; Brown, Br. *J. Cancer* **1993**, 67, 1163). As shown below, the initial one-electron reduction product TPZ$^{\bullet}$ is reoxidised to the starting compound by dioxygen, thereby preventing cytotoxicity in oxic cells.



TPZ is therefore of interest for killing hypoxic cells in tumours, thereby improving overall response during radiation therapy. TPZ also has potential for combination with standard cytotoxic chemotherapy (Dorie and Brown, Cancer Res., **1993**, 53, 4633; Langmuir et al., Cancer Res., **1994**, 54, 2845; Dorie and Brown, Cancer Chemother. Pharmacol., **1997**, 39, 361), with (at least) two mechanisms of therapeutic synergy. The first mechanism is the killing of resistant hypoxic cells (analogous to the mechanism of interaction with radiotherapy), and the second is the interference with repair of chemotherapy-induced DNA damage in hypoxic cells as has been demonstrated for cisplatin (Kovacs et al., *Br. J. Cancer* **1999**, 80, 1245; Peters et al., Cancer Res., 2001, 61: 5425.

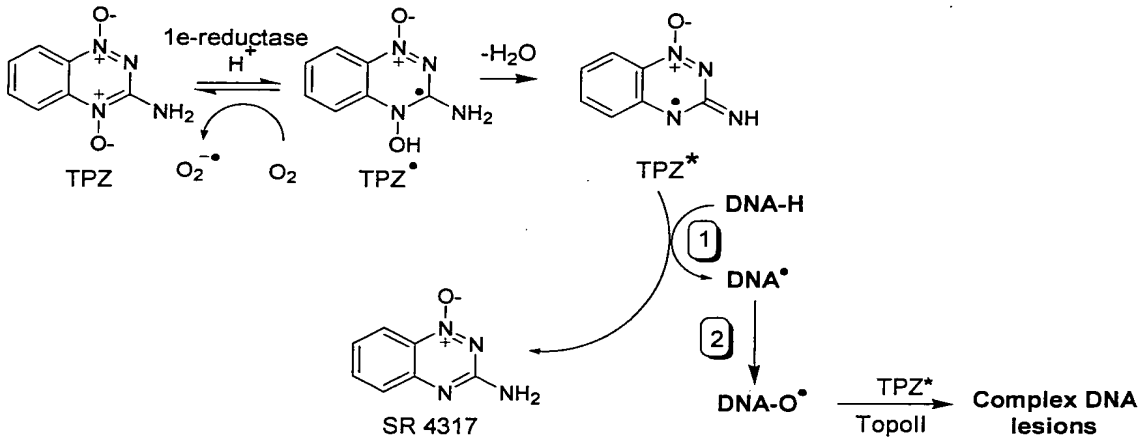
TPZ has already demonstrated significant antitumour activity in early phase human clinical trials in combination with ionising radiation and/or cisplatin chemotherapy (for a review, see Denny and Wilson, *Exp. Opin. Invest. Drugs*, **2000**, 9, 2889), and a multicentre phase III trial of TPZ in combination with cisplatin and radiation for treatment of head and neck tumours is in progress. While TPZ shows promising indications of clinical activity, it also displays considerable toxicity, such as neutropenia, thrombocytopenia, nausea, vomiting, diarrhoea and muscle cramping. These toxicity limitations preclude administration of doses high enough to exploit hypoxia fully during cancer treatment. Although the mechanisms of TPZ toxicity to normal tissues are not fully understood, it is considered that the toxicity arises at least in part because of redox cycling. (Elwell et al., *Biochem. Pharmacol.*, **1997**, 54, 249; Wouters et al., *Cancer Res.*, **2001**, 61, 145) The mechanisms of TPZ toxicity are therefore considered to be distinct from the mechanism of hypoxic cell killing. There would be value in identifying agents capable of enhancing the hypoxic cytotoxic potency of TPZ, without increasing its toxicity to oxic cells, in order to improve its therapeutic selectivity for hypoxic tumour cells.

Recent studies indicate that the cytotoxic species arising from reduction of TPZ under hypoxia is an oxidising radical derived from the initial benzotriazine radical (TPZ•); the ultimate cytotoxin has been variously suggested to be the hydroxyl radical

OH$^{\bullet}$ (Daniels and Gates, *J. Am. Chem. Soc*, **1996**, 118, 3380; Patterson and Taiwo, *Biochem. Pharmacol.*, **2000**, 60, 1933) or the benzotriazinyl radical TPZ$^{\bullet}$ shown in Figure 1 below. (Anderson et al., *J. Am. Chem. Soc*, **2003**, 125, 748). Whatever its identity, the oxidising radical generates DNA radicals which give rise to complex DNA lesions responsible for cytotoxicity in hypoxic cells (Wang et al., *Cancer Res.*, **1992**, 52, **4473**; Siim et al., *Br. J. Cancer* **1996**, 73, 952; Kotandeniya et al., Bioorg. Med. *Chem. Lett.*, **2002**, 12, 2325; Peters and Brown, *Cancer Res.*, **2002**, 62, 5248).

Published studies (Jones and Weinfeld, *Cancer Res.*, **1996**, 56, 1584; Daniels and Gates, *Chem. Res. Toxicol.*, **1998**, 11, 1254) have suggested that TPZ has a dual mechanism of action, with the parent drug being involved in two distinct steps in the generation of DNA damage as represented below in Scheme A.

Scheme A



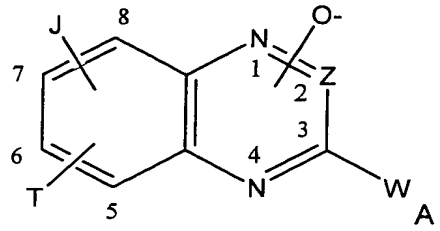
In the first step, the DNA-damaging species, TPZ$^{\bullet}$ or OH$^{\bullet}$, is considered to generate DNA radicals by hydrogen abstraction. In the second step, TPZ itself can further oxidise the initial DNA radicals to generate a more cytotoxic lesion (DNA break). Certain other agents, such as the 1-N-oxide metabolite derived from TPZ (SR 4317, as illustrated in Fig 1), have also been shown to be capable of oxidising DNA radicals of the kind formed by TPZ$^{\bullet}$ (Hwang et al., *Biochemistry*, **1999**, 38, 14248).

It is an object of the present invention to provide a cytotoxic synergistic composition comprising one or more benzoazine-mono-N-oxides, and an effective amount of one or more benzoazine 1,4 dioxides for use as anticancer drugs and as radiosensitizers for cancer therapy in combination with radiation and/or other anticancer drugs, or to at least provide the public with a useful choice.

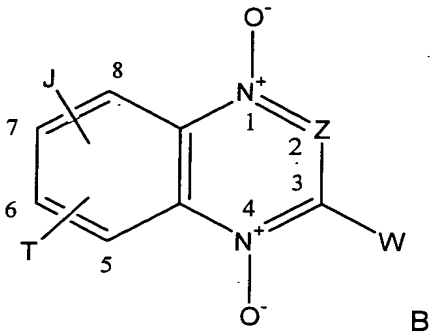
It is also an object of the present invention to provide a range of novel 1,2,4-benzoazine-mono-N-oxides and related analogues, and to their use as potentiators of the cytotoxicity of anticancer drugs and as radiosensitizers for cancer therapy in combination with radiation and/or with other anticancer agents, or to at least provide the public with a useful choice.

SUMMARY OF THE INVENTION

In a first aspect, the present invention provides a cytotoxic synergistic composition, comprising an effective amount of a benzoazine N-mono oxide compound of Formula A or a pharmacologically acceptable salt thereof and an effective amount of a benzoazine 1,4 dioxide compound of Formula B or a pharmacologically acceptable salt thereof



A



B

wherein in Formulae A or B

Z may be selected from N or C-CN, and

wherein in Formula A when Z represents N, the N-oxide moiety occupies one of the 1-, 2-, or 4-positions; and when Z represents C-CN, the N-oxide moiety occupies one of the 1-, or 4-positions;

wherein J in Formulae A or B may represent at one or more of the available carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

wherein each R may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R may also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

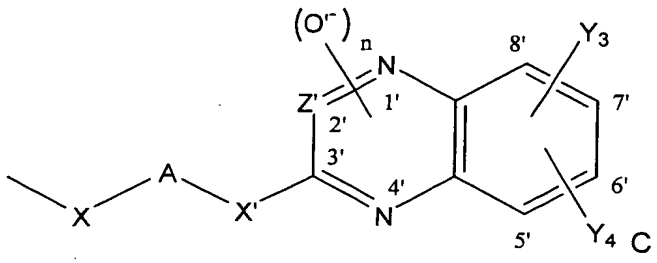
wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein W in Formulae A or B may represent –X-A, wherein -X-A together may represent H, or halogen; or

X may represent O, S, NH, NMe, CH_2, SO, SO_2, CONH, NHCO, CO or CO_2, and

A may represent H, an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR^3, NH_2, NHR^3, NR^3_2, or $N(OH)R^3$ wherein each R^3 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain may be optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, or a pharmacologically acceptable salt thereof, or

W may represent a group of Formula C



wherein in a group of Formula C

n may represent either 1 or 2,

Z' may be selected from N or C-CN, and when Z' represents N, and n represents 1 the N-oxide moiety may occupy one of the 1'-, 2'-, or 4'-positions and when Z' represents C-CN, the N-oxide moiety may occupy one of the 1'-, or 4'-positions; and when Z' represents N or C-CN, and n represents 2 the N-oxide moieties occupy the 1'and 4'-positions

Y_3 and Y_4 may each represent at one or more of the available carbons 5'-8' on the benzo ring the following groups:

halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

wherein each R may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

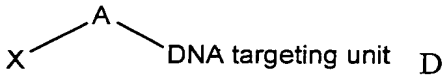
R may also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

X' may represent O, NH, NMe, or CH_2,

A may represent an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR^3, NH_2, NHR^3, NR^3_2, or $N(OH)R^3$ wherein each R^3 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain may be optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, or

W may represent a group of Formula D



D

wherein X may represent NH, NMe, CH_2, or O;
A may represent an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3, NR^3_2, or $N(OH)R^3$ wherein each R^3 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain may be optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and
wherein the DNA-targeting unit is any moiety of a molecular weight below 700 Daltons that has an association constant (K) for binding to double-stranded random sequence DNA of $>10^3$ M^{-1} at an ionic strength of 0.01 M at 20 °C,.

wherein T in Formulae A or B, may represent at one of carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

wherein each R may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R may also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, or

T may represent a group of Formula E

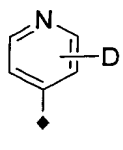
E

wherein X may represent O, S, NH, NMe, CH_2, SO, SO_2, CONH, NHCO, CO, CO_2, or O and

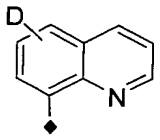
A may represent an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3, NR^3_2, or $N(OH)R^3$ wherein each R^3 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain may be optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein the DNA-targeting unit is any moiety of a molecular weight below 700 Daltons that has an association constant (K) for binding to double-stranded random-sequence DNA of $>10^3$ M^{-1} at an ionic strength of 0.01 M at 20 °C.

Preferably, the DNA targeting agent defined above for a group of Formula D or Formula E may be independently selected from any one of the following wherein the DNA-targeting unit is selected from one of formulae **III- XVII**,



III



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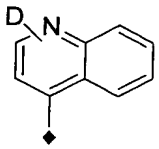

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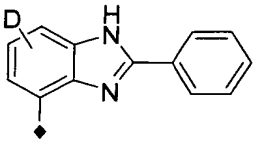

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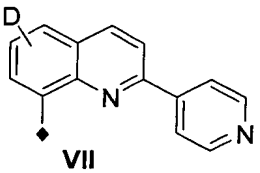

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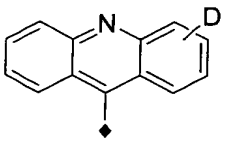

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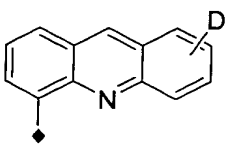

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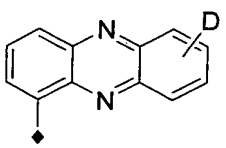
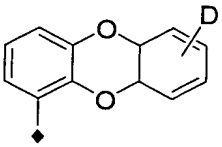
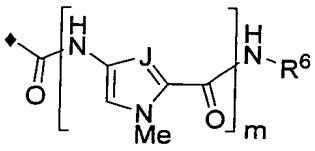


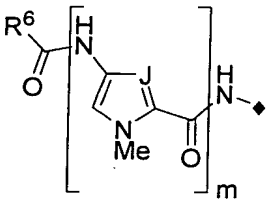
X



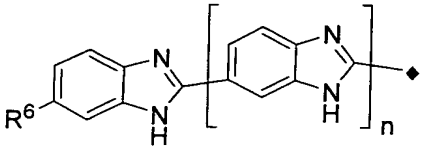
XI



XII



XIII



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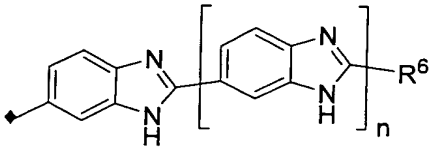

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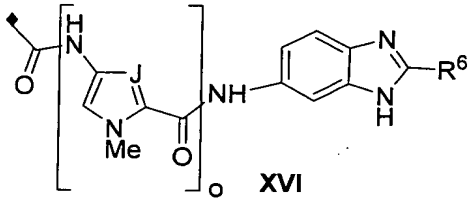
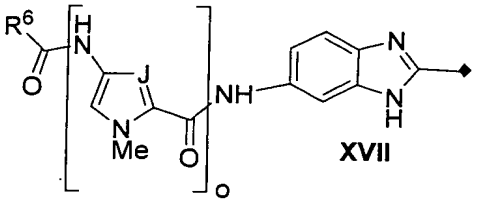


XVI



XVII

wherein in structures **XII-XVII** R^6 may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^7 NO_2,

NH_2, NHR^7, NR^7R^7, SR^7, imidazolyl, R^7-piperazinyl, morpholino, SO_2R^7, CF_3, CN, CO_2H, CO_2R^7, CHO, COR^7, $CONH_2$, $CONHR^7$, $CONR^7R^7$;

R^6 may also be represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^7, NH_2, NHR^7, NR^7R^7, SH, SR^7, imidazolyl, R^7-piperazinyl, morpholino, SO_2R^7, CF_3, CN, CO_2H, CO_2R^7, CHO, COR^7, $CONH_2$, $CONHR^7$, $CONR^7R^7$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^7 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^8, NH_2, NHR^8, $NR^8{}_2$ or $N(OH)R^8$ wherein each R^8 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

D may represent up to four of the following groups as substituents at any available ring carbon position; H, R^9, hydroxy, alkoxy, halogen, NO_2, NH_2, NHR^9, $NR^9{}_2$, SH, SR^9, SO_2R^9, CF_3, CN, CO_2H, CO_2R^9, CHO, COR^9, $CONH_2$, $CONHR^9$ or $CONR^9R^9$, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino, wherein each R^9 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^{10}, NH_2, NHR^{10}, $NR^{10}{}_2$ or $N(OH)R^{10}$ wherein each R^{10} may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

and wherein any available ring carbon position of formulae **III - XVII** may also be optionally replaced by –N- when the valency and configuration of the formula allows, the point of attachment of formulae **III- XVII** to the A group defined above is represented by ♦; and

wherein in formulae **XII, XIII,** , m may be selected from 2, 3 or 4, and

wherein in formulae **XII, XIII, XVI** and **XVII**, J may be selected from CH or N;

and wherein in formulae **XIV** and **XV** n may be selected from 0, 1 or 2;

and wherein in formulae **XVI** and **XVII** o may be selected from 1 and 2.

More preferably the DNA targeting unit is selected from one of formulae **V, VI, VII, VIII, IX or X.** Most preferably, D of the DNA targeting unit of Formulae **III - XI** is H or Me.

Preferably W in Formula A represents $NH(C_1\text{-}C_{12})$ optionally substituted alkyl or a $O(C_1\text{-}C_{12})$ optionally substituted alkyl.

Preferably W in the compound of Formula A represents NH_2, $NHCH_2CH_2NHCH_3$, $NHCH_2CH_2N(CH_3)_2$ or OCH_3.

Preferably, the composition includes a pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser. The pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser should be non-toxic and should not interfere with the efficacy of the active composition. The precise nature of the carrier or other material will depend on the intended route of administration, which may be oral, or by injection such as cutaneous, subcutaneous or by intravenous injection. Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol may be included. A capsule may comprise a solid carrier such as a gelatine. For intravenous, cutaneous or subcutaneous injection, the active composition will be in the form of a parenterally acceptable aqueous solution that is pyrogen-free and has a suitable pH, isotonicity and stability. Those of skill in the art would be able to prepare suitable solutions using for example, isotonic vehicles such as sodium chloride injection, Ringer's injection, lactated Ringer's injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included as required.

It is to be appreciated that the compounds of Formula B are to be taken as including all the DNA-targeted benzotriazine 1,4-dioxides and the methods disclosed for making these compounds as specified in co-pending application New Zealand provisional application NZ 521436 to Auckland Uniservices and the Board of Trustees of the Leland Stanford Junior University. The disclosure of NZ 521436 is hereby incorporated in its entirety.

In a second aspect, there is provided a method of treating a subject in need of cancer therapy, said method comprising the steps of administering to said subject a cytotoxic effective amount of a composition including an effective amount of one or more compounds of Formula A and one or more compounds of formula B as defined above to the tumour cells in said subject.

Preferably, the steps of administration of a compound of Formula A and B may be simultaneous or sequential.

Preferably the tumour cells are in a hypoxic environment.

Preferably, the method includes the further step of administering said composition defined above in combination with one or more other chemotherapeutic agents or treatments, including radiotherapy, either simultaneously, or sequentially, depending on the cancerous condition to be treated.

More preferably the method includes the step of administering radiotherapy to the tumour cells before, during or after the administration of the composition as defined above.

Preferably, the chemotherapeutic agents are selected from Cisplatin or other platinum-based derivatives, Temozolomide or other DNA methylating agents, cyclophosphamide or other DNA alkylating agents, doxorubicin, mitoxandrone, camptothecin or other topoisomerase inhibitors, methotrexate, gemcitabine or other antimetabolites.

While the compositions of the invention will typically be used in cancer therapy of human subjects, they may be used to target tumour cells in other warm blooded animal subjects such as other primates, farm animals such as cattle, and sports animals and pets such as horses, dogs, and cats.

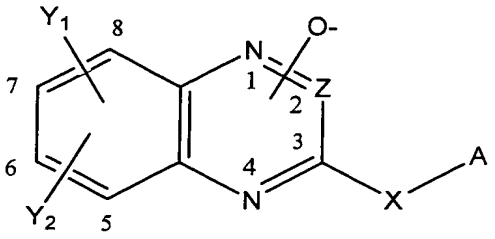
A "cytotoxic effective amount", is to be understood as an amount of the composition including one or more compounds of Formula A and one or more compounds of Formula B as defined above that is sufficient to show benefit to a patient. The actual amount, rate and time-course of administration, will depend on the nature and severity of the disease being treated. Prescription of treatment is within the responsibility of general practitioners and other medical doctors.

A hypoxic environment is to be understood as tissue environments at an oxygen concentration of < 10 μM.

In a third aspect there is provided, the use in the manufacture of a medicament of an effective amount of a composition including an effective amount of one or more

compounds of Formula A or one or more compounds of formula B as defined above for the treatment of a subject in need of cancer therapy.

In a fourth aspect, the present invention provides a compound of Formula I,



I

wherein

Z may be selected from N or C-CN, and when Z represents N, the N-oxide moiety occupies one of the 1-, 2-, or 4-positions; and when Z represents C-CN, the N-oxide moiety occupies one of the 1-, or 4-positions;

Y_1 and Y_2 may each represent at one or more of the available carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

wherein each R may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R may also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein A and X together may represent H, or halogen; or

X may represent O, S, NH, NMe or CH_2 and

A may represent H, an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR^3, NH_2, NHR^3, NR^3_2, or $N(OH)R^3$ wherein each R^3 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain may be optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, or a pharmacologically acceptable salt thereof,

with the proviso that the following compounds are excluded

3-Amino-1,2,4-benzotriazine-1-oxide,

3-Amino-7-trifluoromethyl-1,2,4-benzotriazine-1-oxide,

3-Amino-7-carbamyl-1,2,4-benzotriazine-1-oxide,

3-Amino-7-chloro-1,2,4-benzotriazine-1-oxide,

3-Amino-7-nitro-1,2,4-benzotriazine-1-oxide

3-Chloro-1,2,4-benzotriazine-1-oxide,

3-(3-N,N-Diethylaminopropylamino)- 3-amino-1,2,4-benzotriazine-1-oxide,

3-Chloro-7-nitro-1,2,4-benzotriazine-1-oxide,

7-Nitro-(3-(2-N,N-diethylamino-ethylamino)-1,2,4-benzotriazine-1-oxide,

8-Methoxy-1,2,4-benzotriazin-3-amine 1-oxide,

8-Methyl-1,2,4-benzotriazin-3-amine 1-oxide,

8-Fluoro-1,2,4-benzotriazin-3-amine 1-oxide,

8-Chloro-1,2,4-benzotriazin-3-amine 1-oxide,

8-Trifluoromethyl-1,2,4-benzotriazin-3-amine 1-oxide,

8-(Methylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide,

8-(Butylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide,

3-Amino-1,2,4-benzotriazin-7-ol 1-oxide,

3-Amino-1,2,4-benzotriazin-7-ol 1-oxide,

7-Methyl-1,2,4-benzotriazin-3-amine 1-oxide,

7-Fluoro-1,2,4-benzotriazin-3-amine 1-oxide,

7-Chloro-1,2,4-benzotrazin-3-amine 1-oxide,

7-Trifluoromethyl-1,2,4-benzotriazin-3-amine 1-oxide,

7-(Methylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide,

7-(Butylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide,

7-Nitro-1,2,4-benzotriazin-3-amine 1-oxide,
6-Methoxy-1,2,4-benzotriazin-3-amine 1-oxide,
6-Methyl-1,2,4-benzotriazin-3-amine 1-oxide,
6-Phenyl-1,2,4-benzotriazin-3-amine 1-oxide,
6-Fluoro-1,2,4-benzotriazin-3-amine 1-oxide,
6-Chloro-1,2,4-benzotrazin-3-amine 1-oxide,
6-Trifluoromethyl-1,2,4-benzotriazin-3-amine 1-oxide,
6-(Methylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide,
6-(Butylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide,
5-Methoxy-1,2,4-benzotriazin-3-amine 1-oxide,
5-Methyl-1,2,4-benzotriazin-3-amine 1-oxide,
5-Chloro-1,2,4-benzotriazin-3-amine 1-oxide,
5-Fluoro-1,2,4-benzotriazin-3-amine 1-oxide,
N^7,N^7-Dimethyl-1,2,4-benzotriazine-3,7-diamine 1-oxide,
3-Chloro-1,2,4-benzotriazine 1-oxide,
3-Methyl-1,2,4-benzotriazine 1-oxide,
3-Ethyl-1,2,4-benzotriazine 1-oxide,
3-Phenyl-1,2,4-benzotriazine 1-oxide,
3-(4-Methoxyphenyl)-1,2,4-benzotriazine 1-oxide,
3-Vinyl-1,2,4-benzotriazine 1-oxide,
3-Allyl-1,2,4-benzotriazine 1-oxide,
3-(2-Hydroxyethyl)-1,2,4-benzotriazine 1-oxide,
3-(2-Methoxyethyl)-1,2,4-benzotriazine 1-oxide,
N-Phenyl-1,2,4-benzotriazin-3-amine 1-oxide,
3-Methoxy-1,2,4-benzotriazine 1-oxide,
3-Chloro-7-methyl-1,2,4-benzotriazine 1-oxide,
3-Chloro-7-methoxy-1,2,4-benzotriazine 1-oxide,
1,2,4-benzotriazine 1-oxide,
1,2,4-benzotriazin-3-amine 2-oxide, and
1,2,4-benzotriazin-3-amine 4-oxide.

Preferably, Z is N.

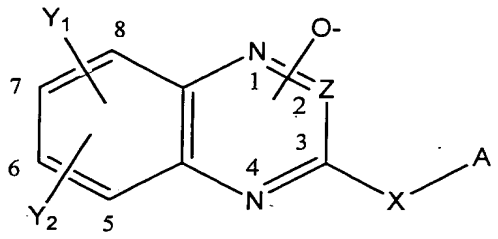
A preferred compound of Formula I is one in which X is NH or CH_2.

A more preferred compound of Formula I is one in which –X-A represents a $NH(C_1-C_{12})$ optionally substituted alkyl or an $O(C_1-C_{12})$ optionally substituted alkyl, such as $NHCH_2CH_2NHCH_3$, $NHCH_2CH_2N(CH_3)_2$ or OCH_3.

A further preferred compound of Formula I is one in which Y_1 and Y_2 each represent H.

A further preferred compound of Formula I' is one in which the N-oxide moiety occupies the 1-position.

In a fifth aspect, there is provided a method of treating a subject in need of cancer therapy, said method comprising the steps of administering to said subject a cytotoxic effective amount of a compound of Formula I



I

wherein

Z may be selected from N or C-CN, and when Z represents N, the N-oxide moiety occupies one of the 1-, 2-, or 4-positions; and when Z represents C-CN, the N-oxide moiety occupies one of the 1-, or 4-positions;

Y_1 and Y_2 may each represent at one or more of the available carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

wherein each R may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R may also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1,

$CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein A and X together may represent H, or halogen; or

X may represent O, S, NH, NMe or CH_2 and

A may represent H, an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3, NR^3_2, or $N(OH)R^3$ wherein each R^3 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain may be optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, or a pharmacologically acceptable salt thereof

to the tumour cells in said subject.

Preferably the tumour cells are in a hypoxic environment.

Preferably, the method includes the further step of administering the compound of Formula I in combination with one or more other chemotherapeutic agents or treatments, including radiotherapy, either simultaneously, or sequentially, depending on the cancerous condition to be treated.

More preferably the method includes the step of administering radiotherapy to the tumour cells before, during or after the administration of the composition as defined above.

Preferably, the chemotherapeutic agents are selected from Cisplatin or other platinum-based derivatives, Temozolomide or other DNA methylating agents, cyclophosphamide

or other DNA alkylating agents, doxorubicin, mitoxandrone, camptothecin or other topoisomerase inhibitors, methotrexate, gemcitabine or other antimetabolites.

While the method of the invention will typically be used in cancer therapy of human subjects, they may be used to target tumour cells in other warm blooded animal subjects such as other primates, farm animals such as cattle, and sports animals and pets such as horses, dogs, and cats.

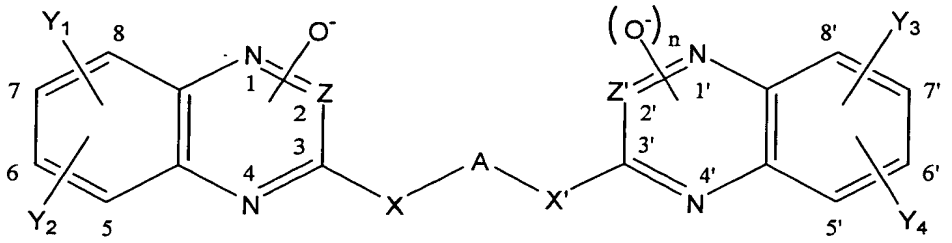
Preferably, the compound of Formula I is administered with a pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser. The pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser should be non-toxic and should not interfere with the efficacy of the active composition. The precise nature of the carrier or other material will depend on the intended route of administration, which may be oral, or by injection such as cutaneous, subcutaneous or by intravenous injection. Pharmaceutical compositions of Formula I for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol may be included. A capsule may comprise a solid carrier such as a gelatine. For intravenous, cutaneous or subcutaneous injection, the active composition will be in the form of a parenterally acceptable aqueous solution that is pyrogen-free and has a suitable pH, isotonicity and stability. Those of skill in the art would be able to prepare suitable solutions using for example, isotonic vehicles such as sodium chloride injection, Ringer's injection, lactated Ringer's injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included as required.

A "cytotoxic effective amount", is to be understood as an amount of a compound of Formula I defined above that is sufficient to show benefit to a patient. The actual amount, rate and time-course of administration, will depend on the nature and severity of the disease being treated. Prescription of treatment is within the responsibility of general practitioners and other medical doctors.

A hypoxic environment is to be understood as tissue environments at an oxygen concentration of < 10 mM.

In a sixth aspect there is provided, the use in the manufacture of a medicament of an effective amount of a compound of Formula I as defined above for the treatment of a subject in need of cancer therapy.

In a seventh aspect the present invention provides a compound of Formula I',



I'

wherein

n may represent either 1 or 2,

Z or Z' may be selected from N or C-CN, and when Z or Z' represents N, and n represents 1 each N-oxide moiety may occupy one of the 1-, 2-, or 4-positions or 1'-, 2'-, or 4'-positions respectively and when Z or Z' represents C-CN, each N-oxide moiety may occupy one of the 1-, or 4-positions or 1'-, or 4'-positions respectively; and when Z' represents N, and n represents 2, the N'-oxide moieties occupy the 1'- and 4'-positions and when Z' represents C-CN, and n represents 2 the N'-oxide moieties occupy the 1'-, and 4'-positions;

Y_1, Y_2, Y_3 and Y_4 may each represent at one or more of the available carbons 5-8 or one or more of the available carbons 5'-8' on the respective benzo ring the following groups:

halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

wherein each R may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R may also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1,

imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X may represent NH, NMe, CH_2, or O;

A may represent an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR^3, NH_2, NHR^3, NR^3_2, or $N(OH)R^3$ wherein each R^3 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain may be optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, or a pharmacologically acceptable salt thereof.

A preferred compound of Formula I' is one in which X is NH or CH_2.

A further preferred compound of Formula I' is one in which Y_1 and Y_2 each represent H.

A further preferred compound of Formula I' is one in which A is $-(CH_2)_2NMe(CH_2)_2-$

A further preferred compound of Formula I' is one in which the N-oxides are positioned at the 1-position.

In an eighth aspect, there is provided a method of treating a subject in need of cancer therapy, said method comprising the steps of administering to said subject a cytotoxic effective amount of a compound of Formula I' as defined above to the tumour cells in said subject.

Preferably the tumour cells are in a hypoxic environment.

Preferably, the method includes the further step of administering the compound of Formula I' in combination with one or more other chemotherapeutic agents or treatments, including radiotherapy, either simultaneously, or sequentially, depending on the cancerous condition to be treated.

More preferably the method includes the step of administering radiotherapy to the tumour cells before, during or after the administration of the composition as defined above.

Preferably, the chemotherapeutic agents are selected from Cisplatin or other platinum-based derivatives, Temozolomide or other DNA methylating agents, cyclophosphamide or other DNA alkylating agents, doxorubicin, mitoxandrone, camptothecin or other topoisomerase inhibitors, methotrexate, gemcitabine or other antimetabolites.

While the method of the invention will typically be used in cancer therapy of human subjects, they may be used to target tumour cells in other warm blooded animal subjects such as other primates, farm animals such as cattle, and sports animals and pets such as horses, dogs, and cats.

Preferably, the compound of Formula I' is administered with a pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser. The pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser should be non-toxic and should not interfere with the efficacy of the active composition. The precise nature of the carrier or other material will depend on the intended route of administration, which may be oral, or by injection such as cutaneous, subcutaneous or by intravenous injection. Pharmaceutical compositions of Formula I' for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol may be included. A capsule may comprise a solid carrier such as a gelatine. For intravenous, cutaneous or subcutaneous injection, the active composition will be in the form of a parenterally acceptable aqueous solution that is pyrogen-free and has a suitable pH, isotonicity and stability. Those of skill in the art would be able to prepare suitable solutions using for example, isotonic vehicles such as sodium chloride

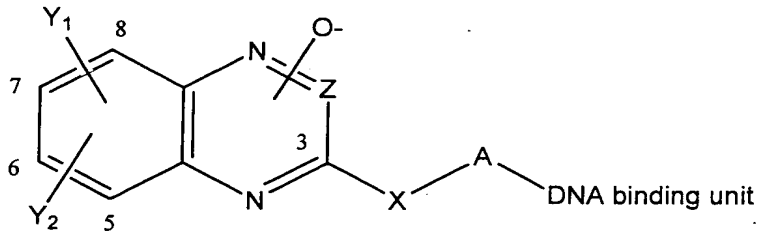
injection, Ringer's injection, lactated Ringer's injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included as required.

A "cytotoxic effective amount", is to be understood as an amount of a compound of Formula I' defined above that is sufficient to show benefit to a patient. The actual amount, rate and time-course of administration, will depend on the nature and severity of the disease being treated. Prescription of treatment is within the responsibility of general practitioners and other medical doctors.

A hypoxic environment is to be understood as tissue environments at an oxygen concentration of < 10 mM.

In a ninth aspect there is provided, the use in the manufacture of a medicament of an effective amount of a compound of Formula I' as defined above for the treatment of a subject in need of cancer therapy.

In a tenth aspect, the present invention provides a compound of Formula II,



II

wherein

Z may be selected from N or C-CN, and when Z represents N, the N-oxide moiety occupies one of the 1-, 2-, or 4-positions; and when Z represents C-CN, the N-oxide moiety occupies one of the 1-, or 4-positions;

Y_1 and Y_2 may each represent at one or more of the available carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

wherein each R may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R may also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X may represent NH, NMe, CH_2, or O;

A may represent an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR^3, NH_2, NHR^3, NR^3_2, or $N(OH)R^3$ wherein each R^3 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain may be optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and

wherein the DNA-targeting unit is any moiety of a molecular weight below 700 Daltons that has an association constant (K) for binding to double-stranded random-sequence DNA of $>10^3$ M^{-1} at an ionic strength of 0.01 M at 20 °C,

or a pharmacologically acceptable salt thereof.

The definition of the DNA targeting unit above refers to double-stranded random-sequence DNA. An example of such double-stranded random-sequence DNA is DNA extracted from calf thymus.

Preferably, Z is N.

A preferred compound of Formula II is one in which X is NH or CH_2.

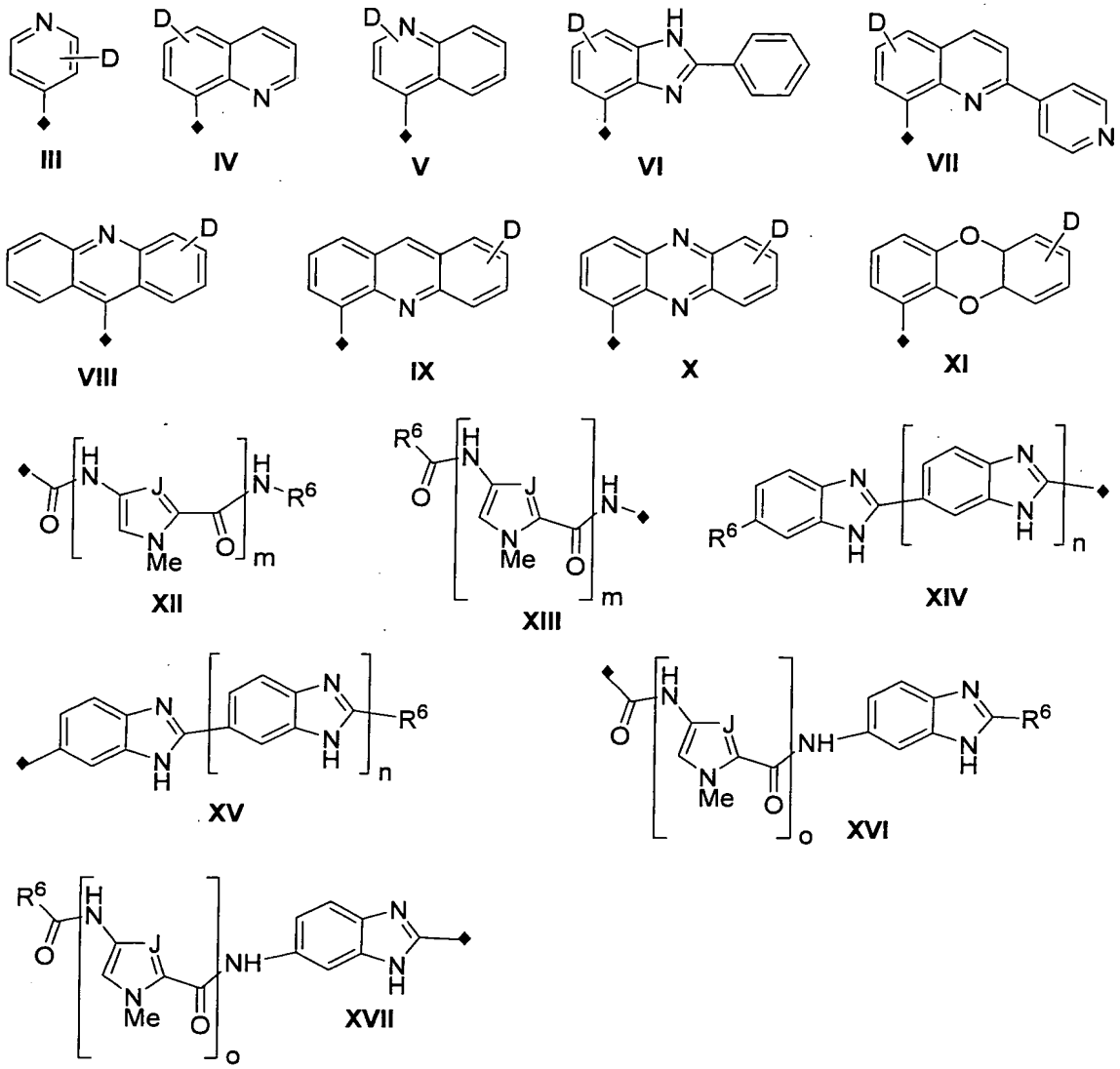
A further preferred compound of Formula II is one in which the N-oxide is at the 1-position

A further preferred compound of Formula II is one in which Y_1 and Y_2 each represent H.

A further preferred compound of Formula II is one in which Y_1 represents Me

A preferred embodiment of Formula II are compounds wherein A is selected from $-(CH_2)_6NH-$, $-(CH_2)_3NH(CH_2)_3NHCO-$, $-(CH_2)_3NMe(CH_2)_3NHCO-$, $-(CH_2)_3NH-$, $-(CH_2)_2NH(CH_2)_2NHCO-$ or $-(CH_2)_2NMe(CH_2)_2NHCO-$.

A further preferred embodiment of Formula II are compounds wherein the DNA-targeting unit is selected from one of formulae **III- XVII**,



wherein in structures **XII-XVII** R^6 may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^7 NO_2, NH_2, NHR^7, NR^7R^7, SR^7, imidazolyl, R^7-piperazinyl, morpholino, SO_2R^7, CF_3, CN, CO_2H, CO_2R^7, CHO, COR^7, $CONH_2$, $CONHR^7$, $CONR^7R^7$;

R^6 may also be represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^7, NH_2, NHR^7, NR^7R^7, SH, SR^7, imidazolyl, R^7-piperazinyl, morpholino, SO_2R^7, CF_3, CN, CO_2H, CO_2R^7, CHO, COR^7, $CONH_2$, $CONHR^7$, $CONR^7R^7$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^7 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^8, NH_2, NHR^8, NR^8_2 or $N(OH)R^8$ wherein each R^8 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

D may represent up to four of the following groups as substituents at any available ring carbon position; H, R^9, hydroxy, alkoxy, halogen, NO_2, NH_2, NHR^9, NR^9_2, SH, SR^9, SO_2R^9, CF_3, CN, CO_2H, CO_2R^9, CHO, COR^9, $CONH_2$, $CONHR^9$ or $CONR^9R^9$, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino, wherein each R^9 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^{10}, NH_2, NHR^{10}, NR^{10}_2 or $N(OH)R^{10}$ wherein each R^{10} may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

and wherein any available ring carbon position of formulae **III - XVII** may also be optionally replaced by –N- when the valency and configuration of the formula allows, the point of attachment of formulae **III- XVII** to the A group defined above is represented by ♦; and

wherein in formulae **XII, XIII,** , m may be selected from 2, 3 or 4, and

wherein in formulae **XII, XIII, XVI** and **XVII**, J may be selected from CH or N;

and wherein in formulae **XIV** and **XV** n may be selected from 0, 1 or 2;

and wherein in formulae **XVI** and **XVII** o may be selected from 1 and 2.

A preferred embodiment of formula II is one in which the DNA targeting unit is selected from one of formulae **V, VI, VII, VIII, IX or X.**

A preferred embodiment of formula II is one in which D of the DNA targeting unit of Formulae **III - XI** is H or Me.

Further preferred compounds of formula II include the following

wherein X is NH-, Y is H, Z is N, position 1-oxide, A is $-(CH_2)_2NH(CH_2)_2NHCO-$, the DNA targeting unit represents formula IX and D is H;

wherein X is NH-, Y is H, Z is N, position 1-oxide, A is $-(CH_2)_3NH(CH_2)_3NHCO-$, the DNA targeting unit represents formula IX and D is H;

wherein X is NH-, Y is H, Z is N, position 1-oxide, A is $-(CH_2)_2NMe(CH_2)_2NHCO-$, the DNA targeting unit represents formula IX and D is H;

wherein X is NH-, Y is 6-Me, Z is N, position 1-oxide, A is $-(CH_2)_2NMe(CH_2)_2NHCO-$, the DNA targeting unit represents formula IX and D is H;

wherein X is NH-, Y is H, Z is N, position 1-oxide, A is $-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula IX and D is H;

wherein X is NH-, Y is 6-Me, Z is N, position 1-oxide, A is $-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula IX and D is H;

wherein X is NH-, Y is H, Z is N, position 1-oxide, A is $-(CH_2)_2NMe(CH_2)_2NHCO-$, the DNA targeting unit represents formula IX and D is Me;

wherein X is NH-, Y is H, Z is N, position 1-oxide, A is $-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula IX and D is Me.

In an eleventh aspect, there is provided a method of treating a subject in need of cancer therapy, said method comprising the steps of administering to said subject a cytotoxic effective amount of a compound of Formula II as defined above to the tumour cells in said subject.

Preferably the tumour cells are in a hypoxic environment.

Preferably, the method includes the further step of administering the compound of Formula II in combination with one or more other chemotherapeutic agents or treatments, including radiotherapy, either simultaneously, or sequentially, depending on the cancerous condition to be treated.

More preferably the method includes the step of administering radiotherapy to the tumour cells before, during or after the administration of the composition as defined above.

Preferably, the chemotherapeutic agents are selected from Cisplatin or other platinum-based derivatives, Temozolomide or other DNA methylating agents, cyclophosphamide

or other DNA alkylating agents, doxorubicin, mitoxandrone, camptothecin or other topoisomerase inhibitors, methotrexate, gemcitabine or other antimetabolites.

While the method of the invention will typically be used in cancer therapy of human subjects, they may be used to target tumour cells in other warm blooded animal subjects such as other primates, farm animals such as cattle, and sports animals and pets such as horses, dogs, and cats.

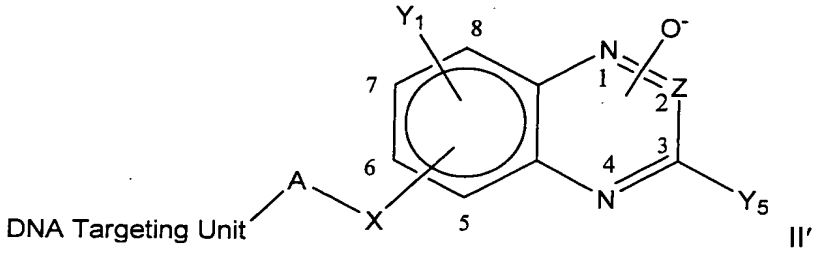
Preferably, the compound of Formula II is administered with a pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser. The pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser should be non-toxic and should not interfere with the efficacy of the active composition. The precise nature of the carrier or other material will depend on the intended route of administration, which may be oral, or by injection such as cutaneous, subcutaneous or by intravenous injection. Pharmaceutical compositions of Formula II for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol may be included. A capsule may comprise a solid carrier such as a gelatine. For intravenous, cutaneous or subcutaneous injection, the active composition will be in the form of a parenterally acceptable aqueous solution that is pyrogen-free and has a suitable pH, isotonicity and stability. Those of skill in the art would be able to prepare suitable solutions using for example, isotonic vehicles such as sodium chloride injection, Ringer's injection, lactated Ringer's injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included as required.

A "cytotoxic effective amount", is to be understood as an amount of a compound of Formula II defined above that is sufficient to show benefit to a patient. The actual amount, rate and time-course of administration, will depend on the nature and severity of the disease being treated. Prescription of treatment is within the responsibility of general practitioners and other medical doctors.

A hypoxic environment is to be understood as tissue environments at an oxygen concentration of < 10 mM.

In a twelth aspect there is provided, the use in the manufacture of a medicament of an effective amount of a compound of Formula II as defined above for the treatment of a subject in need of cancer therapy.

In a thirteenth aspect, the present invention provides a compound of Formula II',



II'

wherein

Z may be selected from N or C-CN, and when Z represents N, the N-oxide moiety occupies one of the 1-, 2-, or 4-positions; and when Z represents C-CN, the N-oxide moiety occupies one of the 1-, or 4-positions;

Y_1 may represent at one or more of the available carbons 5-8 on the benzo ring the following groups:
halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

Y_5 may be selected from the following groups halo, H, R, OR, NH_2, NHR, NR_2, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

wherein each R of groups Y_1 and Y_5 may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R may also be represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1,

imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S; wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X may represent NH, NMe, CH_2, S, SO, SO_2, CONH, NHCO, CO, CO_2, or O;

A may represent an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR^3, NH_2, NHR^3, NR^3_2 or $N(OH)R^3$ wherein each R^3 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{2-12} alkyl chain may be optionally interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and

wherein the DNA-targeting unit is any moiety of a molecular weight below 700 Daltons that has an association constant (K) for binding to double-stranded random-sequence DNA of $>10^3$ M^{-1} at an ionic strength of 0.01 M at 20 °C,

or a pharmacologically acceptable salt thereof.

The definition of the DNA targeting unit above refers to double-stranded random-sequence DNA. An example of such double-stranded random-sequence DNA is DNA extracted from calf thymus.

Preferably, Z is N.

A preferred compound of Formula II' is one in which X is O or CH_2

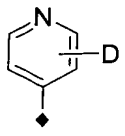
A further preferred compound of Formula II' is one in which the N-oxide is at the 1-position

A further preferred compound of Formula II' is one in which Y_1 represents H

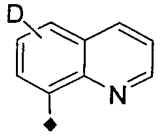
A further preferred compound of Formula II' is one in which Y_5 represents NHR

A preferred embodiment of Formula II are compounds wherein A is selected from $-(CH_2)_6NH-$, $-(CH_2)_3NH(CH_2)_3NHCO-$, $-(CH_2)_3NMe(CH_2)_3NHCO-$, $-(CH_2)_3NH-$, $-(CH_2)_2NH(CH_2)_2NHCO-$ or $-(CH_2)_2NMe(CH_2)_2NHCO-$.

A further preferred embodiment of Formula II are compounds wherein the DNA-targeting unit is selected from one of formulae **III- XVII**,



III



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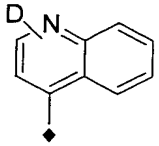

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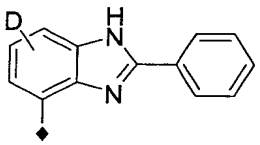

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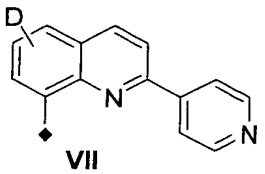

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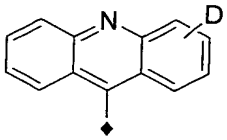

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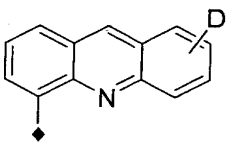
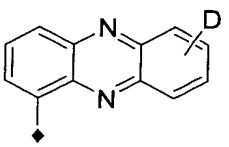
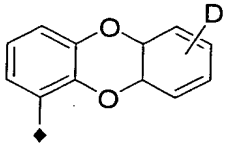


IX



X



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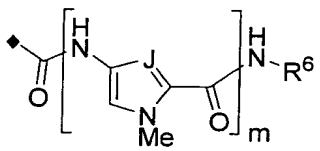

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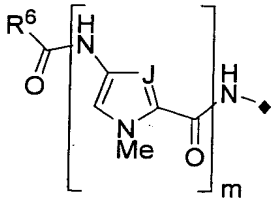

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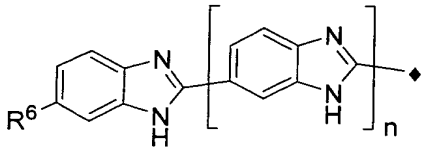
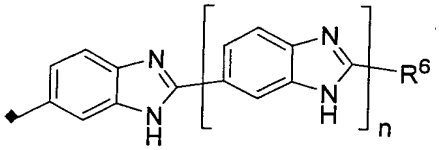
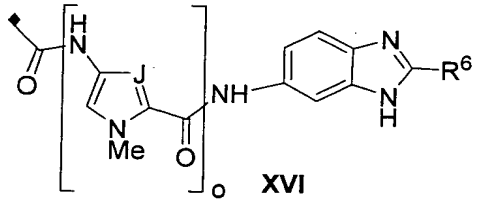


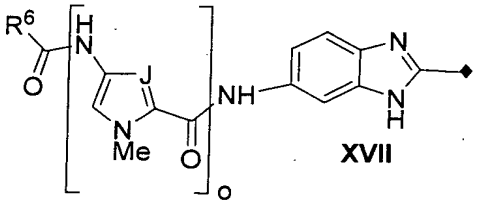
XIV



XV



XVI



XVII

wherein in structures **XII - XVII** R^6 may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^7 NO_2, NH_2, NHR^7, NR^7R^7, SR^7, imidazolyl, R^7-piperazinyl, morpholino, SO_2R^7, CF_3, CN, CO_2H, CO_2R^7, CHO, COR^7, $CONH_2$, $CONHR^7$, $CONR^7R^7$;

R^6 may also be represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^7, NH_2, NHR^7, NR^7R^7, SH, SR^7, imidazolyl, R^7-piperazinyl, morpholino, SO_2R^7, CF_3, CN, CO_2H, CO_2R^7, CHO, COR^7, $CONH_2$, $CONHR^7$, $CONR^7R^7$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^7 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^8, NH_2, NHR^8, $NR^8{}_2$ or $N(OH)R^{98}$ wherein each R^8 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

D may represent up to four of the following groups as substituents at any available ring carbon position; H, R^9, hydroxy, alkoxy, halogen, NO_2, NH_2, NHR^9, $NR^9{}_2$, SH, SR^9, SO_2R^9, CF_3, CN, CO_2H, CO_2R^9, CHO, COR^9, $CONH_2$, $CONHR^9$ or $CONR^9R^9$, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino, wherein each R^9 independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^{10}, NH_2, NHR^{10}, $NR^{10}{}_2$ or $N(OH)R^{10}$ wherein each R^{10} may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

and wherein any available ring carbon position of formulae **III- XVII** may also be optionally replaced by –N- when the valency and configuration of the formula allows, the point of attachment of formulae **III- XVII** to the A group defined above is represented by ♦; and

wherein in formulae **XII** and **XIII**, m may be selected from 2, 3 or 4,
and wherein in formulae **XII, XIII, XVI or XVII** J may be selected from CH or N; and
wherein in formulae **XIV** and **XV** n may be selected from 0, 1 or 2, and
wherein in formulae **XVI** and **XVII** o may be selected from 1 or 2.

A preferred embodiment of formula II′ is one in which the DNA targeting unit is selected from one of formulae IV - X.

A preferred embodiment of formula II′ is one in which D of the DNA targeting unit of Formulae III – XI is H or Me.

Preferred compounds of formula II′ include the following

wherein X is CH_2-, Y_1 is H, Y_5 is $NHCH_2CH_2OMe$, Z is –N-, A is – $(CH_2)NMe(CH_2)_2NHCO$-, the DNA targeting unit represents formula IX and D is H;

wherein X is CH_2-, Y_1 is H, Y_5 is $NHCH_2CH_2OMe$, Z is –N-, A is– $(CH_2)_2NH(CH_2)_3NHCO$-, the DNA targeting unit represents formula IX and D is H;

wherein X is CH_2-, Y_1 is H, Y_5 is $NHCH_2CH_2OMe$, Z is –N-, A is – $(CH_2)NMe(CH_2)_2NHCO$-, the DNA targeting unit represents formula IX and D is Me;

wherein X is CH_2-, Y_1 is H, Y_5 is $NHCH_2CH_2OMe$, Z is –N-, A is – $(CH_2)_2NMe(CH_2)_3NHCO$-, the DNA targeting unit represents formula IX and D is Me;

wherein X is CH_2-, Y_1 is H, Y_5 is $NHCH_2CH_2OMe$, Z is –N-, A is– $(CH_2)NMe(CH_2)_2NHCO$-, the DNA targeting unit represents formula X and D is Me;

wherein X is CH_2-, Y_1 is H, Y_5 is $NHCH_2CH_2OMe$, Z is –N-, A is– $(CH_2)_2NH(CH_2)_3NHCO$-, the DNA targeting unit represents formula X and D is Me;

In a fourteenth aspect, there is provided a method of treating a subject in need of cancer therapy, said method comprising the steps of administering to said subject a cytotoxic effective amount of a compound of Formula II' as defined above to the tumour cells in said subject.

Preferably the tumour cells are in a hypoxic environment.

Preferably, the method includes the further step of administering the compound of Formula II' in combination with one or more other chemotherapeutic agents or treatments, including radiotherapy, either simultaneously, or sequentially, depending on the cancerous condition to be treated.

More preferably the method includes the step of administering radiotherapy to the tumour cells before, during or after the administration of the composition as defined above.

Preferably, the chemotherapeutic agents are selected from Cisplatin or other platinum-based derivatives, Temozolomide or other DNA methylating agents, cyclophosphamide or other DNA alkylating agents, doxorubicin, mitoxandrone, camptothecin or other topoisomerase inhibitors, methotrexate, gemcitabine or other antimetabolites.

While the method of the invention will typically be used in cancer therapy of human subjects, they may be used to target tumour cells in other warm blooded animal subjects such as other primates, farm animals such as cattle, and sports animals and pets such as horses, dogs, and cats.

Preferably, the compound of Formula II' is administered with a pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser. The pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser should be non-toxic and should not interfere with the efficacy of the active composition. The precise nature of the carrier or other material will depend on the intended route of administration, which may be oral, or by injection such as cutaneous, subcutaneous or by intravenous injection. Pharmaceutical compositions of Formula II' for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol may be included. A capsule may comprise a solid carrier such as a gelatine. For intravenous, cutaneous or subcutaneous injection, the active composition will be in the form of a parenterally acceptable aqueous solution that is pyrogen-free and has a suitable pH, isotonicity and stability. Those of skill in the art would be able to prepare suitable solutions using for example, isotonic vehicles such as sodium chloride injection, Ringer's injection, lactated Ringer's injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included as required.

A "cytotoxic effective amount", is to be understood as an amount of a compound of Formula II' defined above that is sufficient to show benefit to a patient. The actual amount, rate and time-course of administration, will depend on the nature and severity

of the disease being treated. Prescription of treatment is within the responsibility of general practitioners and other medical doctors.

A hypoxic environment is to be understood as tissue environments at an oxygen concentration of < 10 mM.

In a fifteenth aspect there is provided, the use in the manufacture of a medicament of an effective amount of a compound of Formula II' as defined above for the treatment of a subject in need of cancer therapy.

In a sixteenth aspect of the invention, there is provided a method of potentiating the cytotoxicity of an amount of a compound of Formula B or a composition including Formula B as defined above, which has been administered to a subject in need of cancer therapy, by administering to said subject a compound of Formula A or a composition including Formula A as defined above.

Preferably the method potentiates the hypoxic cytotoxicity of an amount of a compound of Formula B.

Preferably, the method includes the further step of administering to said subject the compound of Formula A or a composition including Formula A in combination with one or other chemotherapeutic agents or treatments defined above, including radiotherapy, either simultaneously, or sequentially depending on the cancerous condition to be treated.

More preferably, the method includes the step of administering radiotherapy to the subject, before, during or after the administration of said compound of Formula A or said composition including Formula A.

In a seventeenth aspect of the invention, there is provided a method of potentiating the cytotoxicity of one or more chemotherapeutic agents as defined above, administered to a subject, by further administering to said subject a compound of Formula A or a composition including Formula A as defined above.

Preferably the method potentiates the hypoxic cytotoxicity of the one or more chemotherapeutic agents.

Preferably, the method includes the further step of administering radiotherapy to said subject, either simultaneously, or sequentially depending on the cancerous condition to be treated.

More preferably, the method includes the step of administering radiotherapy to the subject, before, during or after the administration of said compound of Formula A or said composition including Formula A.

It is to be recognised that certain compounds of the present invention may exist in one of more different enantiomeric or diastereomeric forms. It is to be understood that the enantiomeric or diasteriomeric forms are included in the above aspects of the invention.

The term halo or halogen group used throughout the specification is to be taken as meaning a fluoro, chloro, bromo or iodo group.

Further aspects of the present invention will become apparent from the following description given by way of example only and with reference to the accompanying Figures and synthetic schemes, in which:

Figure 1 shows the potentiation of the anoxic cytotoxicity of the benzotriazine di-N-oxide tirapazamine (TPZ; 30 μM) by the corresponding 1-oxide SR4317 in stirred single cell suspensions of HT29 human colon carcinoma cells at $5x10^5$ cells/ml. Cultures were maintained at <10 ppm O_2 under a continuously-flowing stream of 5%CO_2 in nitrogen and were sampled at intervals to determine plating efficiency. SR4317 alone was non-toxic up to its solubility limit (ca 1 mM).

Figure 2 shows lack of potentiation of the cytotoxicity of TPZ by SR4317 under aerobic conditions. Experimental conditions were as for Figure 2, except that the gas phase was 5% CO_2 in air. Values are means and error bars are ranges for duplicate cultures.

Figure 3 shows potentiation of the cytotoxicity of TPZ (30 μM) against anoxic HT29 cells (5×10^5/ml) by SR 4317, misonidazole and metronidazole. Drug exposure time was 1 hr. Error bars represent the range for duplicate determinations.

Figure 4 shows radiosensitisation of anoxic HT29 cells (5×10^5/ml) by 0.6 mM SR 4317 (squares), 0.6 mM misonidazole (triangles), and 0.6 mM metronidazole (diamonds). Anoxic cell suspensions were irradiated 5 min after addition of pre-equilibrated anoxic drug solutions. Data are shown for duplicate determinations, and are fitted using a linear-quadratic model

Figure 5A shows histology of an HT29 MCL, stained with haematoxylin and eosin, and apparatus (diffusion chamber) for measurement of transport through MCLs. Compounds are added to the donor compartment, along with ^{14}C-urea as an internal standard, and diffusion into the receiver compartment is monitored by HPLC and scintillation counting.

Figure 5B shows transport of SR 4317 (200 µM) and TPZ (50 µM) through oxic and hypoxic HT-29 MCLs (*ca* 160 µm in thickness). The concentrations in the Receiver compartment (normalised against the initial concentration in the Donor compartment) are plotted against those of the flux marker ^{14}C-urea to account for small differences in thickness of the MCLs. The fitted diffusion coefficients for TPZ (n=12) and SR 4317 (n=2) are: 3.97 and 32.7×10^{-7} cm^2sec^{-1}, respectively.

Figure 6 shows plasma pharmacokinetics of TPZ (left panel) and SR 4317 (right panel) after intraperitoneal administration of TPZ (270 µmol/kg; circles), SR 4317 (750 µmol/kg; squares), or co-administration of TPZ + SR 4317 (triangles) at these doses to CD-1 mice bearing HT29 human tumour xenografts.

Figure 7 shows potentiation of the cytotoxicity of TPZ (133 µmol/kg) against hypoxic (radioresistant) cells in HT29 tumours. Animals with subcutaneous tumours (ca 300 mg) received whole body radiation (RAD; 20 Gy) to sterilise oxygenated tumour cells. Activity of drugs against the hypoxic survivors was determined by intraperitoneal administration of solutions in 5% DMSO/saline 5 min after radiation, using TPZ alone (133 µmol/kg) or in combination with SR 4317 (1000 µmol/kg). Tumours were excised 18 hr after treatment, dissociated enzymatically, and plated to determine the number of clonogenic survivors. Values are geometric means and error bars are standard errors of the mean. Horizontal lines show historical values for untreated controls and radiation only (solid lines are means, dashed lines are 95% confidence limits. p values were determined by one-way ANOVA using only data within this experiment.

DETAILED DESCRIPTION OF THE INVENTION

The inventors have demonstrated that the cytotoxicity of tirapazamine (TPZ) to hypoxic tumour cells can surprisingly be increased quite markedly by simultaneous exposure to SR 4317, as illustrated for HT29 tumour cells in culture in Fig.1. Advantageously, SR 4317 does not potentiate the aerobic toxicity of TPZ (Fig 2), and therefore can be used to increase the hypoxic selectivity of the latter.

This observation provides evidence that the second (DNA radical oxidation) step in the dual action of TPZ as illustrated in Scheme A in the background of the invention is a limiting factor for its hypoxic cytotoxicity. It also demonstrates that the therapeutic utility of TPZ and related analogues could, in principle, be improved by simultaneous exposure to SR 4317 or an analogous DNA radical oxidant.

The inventors have also shown that DNA radical oxidising agents other than TPZ (illustrated by the nitroimidazoles metronidazole and misonidazole) are able to potentiate the hypoxic cytotoxicity of TPZ, although with lower dose potency than SR 4317 (Fig 4). Unexpectedly, comparison of the ability of these agents to radiosensitize hypoxic HT29 cells (Fig 5), under the same conditions as for the TPZ potentiation experiments, shows that the structure-activity relationship for TPZ potentiation (potency SR 4317 > metronidazole = misonidazole) is different from that for radiosensitization (misonidazole > metronidazole = SR4317). The inventors therefore consider that there is a special feature of the benzoazine N-oxide system for potentiation of the hypoxic cytotoxicity of TPZ and its related analogues.

The inventors have also investigated the extravascular transport properties (tissue diffusion characteristics) of SR 4317 to assess whether it can diffuse well enough to reach hypoxic cells in tumours efficiently. This study used the multicellular layer (MCL) assay (Hicks et al., *Int. J. Radiat. Oncol., Biol., Phys.*, **1998**, 42, 641; Hicks et al., *J. Pharmacol. Exper. Ther.*, **2001**, 297, 1088), developed in this laboratory. Transport of SR 4317 through hypoxic MCLs grown from HT29 cells was faster than for TPZ Fig 5, which indicates its ability to reach hypoxic cells in tumours.

The plasma pharrmacokinetics of SR 4317 and TPZ were determined in C_3H mice, alone and in combination (Fig 6), to assess whether therapeutic concentrations of SR 4317 can be achieved in mice. The maximum SR 4317 concentration in plasma, after

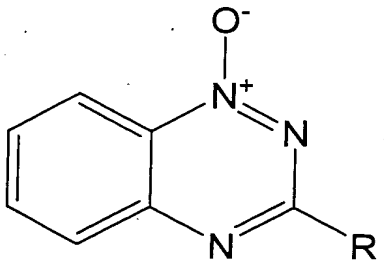
co-administration of the two compounds, was ca 200 μM with a slow clearance over the first two hours. Based on the *in vitro* results in Fig 3 (showing significant potentiation of TPZ cytotoxicity with SR 4317 at 100 μM for 1 hr), and the efficient tissue penetration of SR 4317 (Fig 4), the plasma concentration profile would appear to be high enough to cause potentiation of TPZ hypoxic cytotoxicity in tumours.

The utility of SR 4317 as a potentiator of the hypoxic cytotoxicity of TPZ was assessed in an *in vivo* model (HT29 tumour xenografts) as illustrated in Fig 7. In this experiment tumour response was determined by excising tumours 18 hr after treatment and quantifying the number of clonogenic survivors by plating *in vitro.* TPZ was administered at a sub-efficacious dose (0.133 mmol/kg), 5 minutes after whole body radiation (20 Gy). As anticipated from earlier experiments, this dose of TPZ did not result in statistically significant killing of the (hypoxic) cells surviving radiation. Adding SR 4317 (1 mmol/kg) to this combination provided activity that was now greater than radiation alone ($p < 0.01$ by one way ANOVA), and the difference between radiation + TPZ vs radiation + TPZ + SR 4317 was also significant ($p < 0.05$). No significant cytotoxicity was observed when the two compounds were administered in the absence of irradiation, indicating lack of activity against aerobic cells in tumours (Fig 7). This experiment demonstrates selective potentiation of the hypoxic cytotoxicity of TPZ in tumours.

It is envisaged that further potentiation over and above that seen with SR 4317 could be readibly achieved. This is because SR4317 has only modest aqueous solubility (ca 800 μM) and provides relatively low plasma concentrations in mice.

The following table shows potentiation of anoxic cytotoxicity results using TPZ and benzotriazine-1-oxides.

Table 1: Potentiation of the anoxic cytotoxicity of tirapazamine by benzotriazine-1-oxides as assessed using an IC50 assay (HT29 cell line)



Compound		Solubility limit (mM)[a]	IC_{50} of potentiator (mM)[b]	TPZ potentiation test[c]	
No (SN)	R			Conc of potentiator (mM)	TPR
3 (SR 4317)	NH_2	0.8	>0.5	0.5	2.0
25	$NHCH_2CN$	0.3	>0.3	0.2	1.9
130	$NHCH_2CH_2NHCH_3$	3	2.3	1.0	6.1
37	$NHCH_2CH_2N(CH_3)_2$	1	>1	1.0	13.9
44	$NH(CH_2)_3N(CH_3)_2$	3.0	0.83	0.3	1.2
56	Et	3.0	>3	3.0 [d]	1.3
61	CH_2CH_2OH	3.0	>3	3	1.2
71	OCH_3	0.3	>0.3	0.3	3.3

[a] Approximate solubility limit in Alpha MEM culture medium containing 5% fetal calf serum, determined by dilution from DMSO stock solutions

[b] Concentration of potentiator required to decrease density of HT29 colon carcinoma cells to 50% of controls on the same 96-well plate following 4 hr exposure under anoxic conditions (anaerobic chamber). Cell density was determined by staining with sulphorhodamine B five days after washing out the compounds.

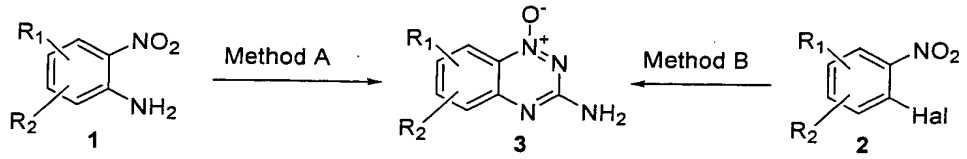
[c] The IC_{50} of TPZ (4 hr anoxic exposure of HT29 cells) was determined in the presence and absence of the potentiator at the indicated concentration. Controls with potentiator only indicated that these concentrations were non-toxic. TPR (TPZ potentiation ratio) = TPZ IC_{50} without potentiator/TPZ IC_{50} with potentiator (on the same 96 well plate). The IC_{50} for TPZ alone in this experiment was 0.0068 ± 0.0010 μM (mean ± sem, n=4)

[d] Approximate concentration (slight precipitation in the IC_{50} assay).

Methods for preparing compounds of Formulas I, I', II, and II' of the invention.

Reaction of the appropriately substituted 2-nitroanilines **1** with cyanamide, followed by cyclization of the intermediate guanidine with NaOH (Method A) gave corresponding 1-oxides **3**. In several instances (7-CF_3, 7-NO_2, 5-Cl, 8-F), it was necessary to use an alternative method (Method B) involving reaction of 2-halonitrobenzenes (**2**) with guanidine, followed by cyclization under basic conditions. This gave 1-oxides **3** in modest yield (Scheme 1).

Schem 1



Method A Reagents:

a) NH_2CN, HCl;

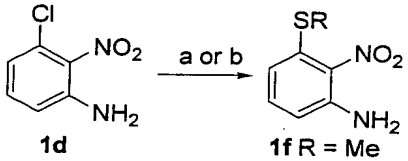
b) NaOH;

Method B Reagents:

a) Guanidine.HCl, tBuOK.

The sulfides **1f** and **1g** were prepared by substitution of 3-chloro-2-nitroaniline **1d** (Scheme 2).

Scheme 2



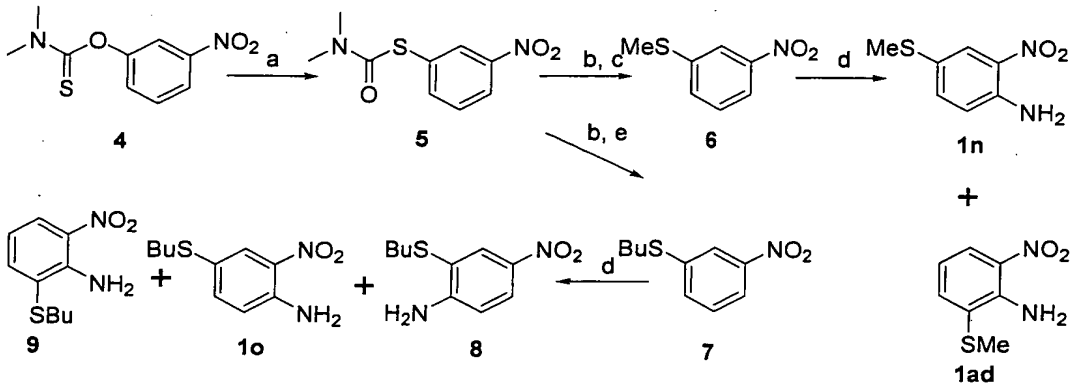
Reagents:

a) MeSLi, DMF;

b) BuSLi, DMF.

The sulfide **1n** and **1o** were prepared using the Newman-Kwart rearrangement (Newman & Karnes, *J. Org. Chem.* **1966**, *31*, 3980-3984) and vicarious nucleophilic substitution (V_NS) (Seko, et al., *J. Chem. Soc. Perkin Trans. 1* **1999**, 1437-1444; Makosza & Bialecki, *J. Org. Chem.* **1998**, *63*, 4878-4888) (Scheme 3). Thus, isomerisation of *O*-thiocarbamate **4** gave *S*-thiocarbamate **5**, which was hydrolysed, and the intermediate thiol alkylated with MeI to give sulfide **6**. V_NS Reaction of **6** with $NH_2OMe.HCl$ gave nitroanilines **1n** and **1ad**. A similar sequence from **5** gave butylsulfanylnitroaniline **1o** as well as the isomeric **8** and **9**.

Scheme 3



Reagents:

a) neat, 220 °C;

b) KOH, MeOH;

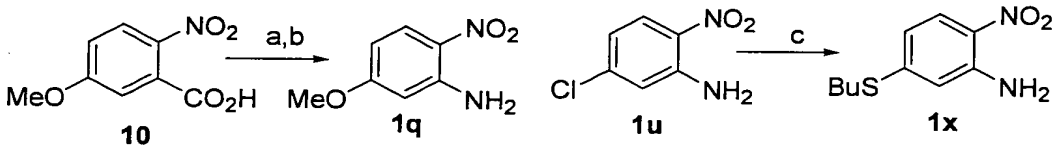
c) Me_2SO_4, KOH, MeOH;

d) $NH_2OMe.HCl$, KOtBu, CuCl, DMF;

e) nBuBr, K_2CO_3, DMF.

Nitroaniline **1q** was prepared by Curtius rearrangement of 5-methoxy-2-nitrobenzoic acid (**10**) (Scheme 4). Nitroaniline **1x** was prepared by nucleophilic displacement of **1u** (Scheme 4).

Scheme 4



Reagents:

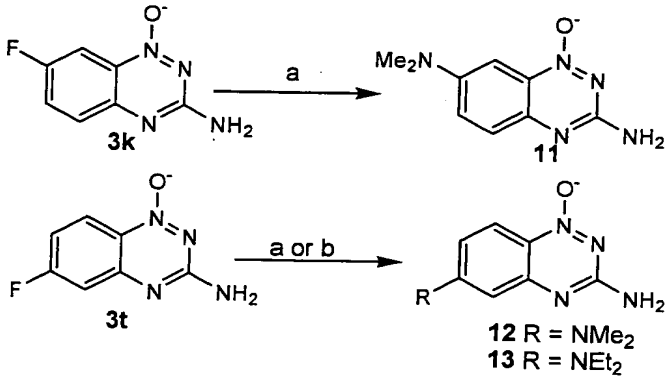
a) Diphenylphosphorylazide, Et_3N, tBuOH;

b) HCl, MeOH;

c) NBuSLi, DMF.

Displacement of the fluoride **3k** with dimethylamine gave 1-oxide **11** (Scheme 5) and similarly reaction of fluoride **3t** with either dimethylamine or diethylamine gave **12** and **13**, respectively.

Scheme 5



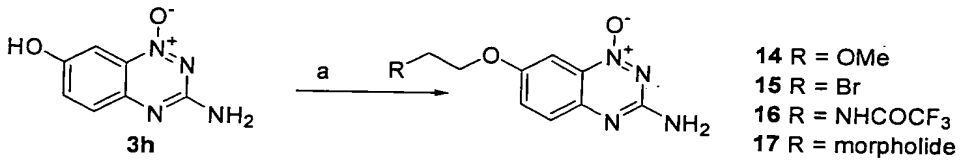
Reagents:

a) NMe_2, MeCN;

b) NEt_2, MeCN.

Alkylation of the 7-hydroxy-1-oxide **3h** with bromides gave compounds **14-17** (Scheme 6).

Scheme 6



Reagents:

For **14**: $BrCH_2CH_2OMe$, K_2CO_3, DMF;

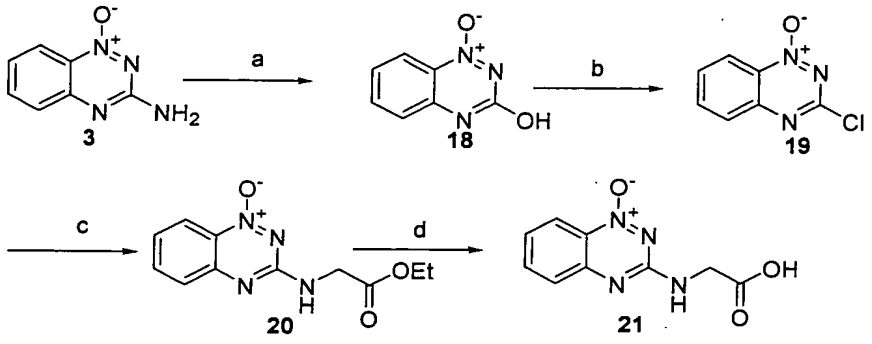
For **15**: $BrCH_2CH_2Br$, K_2CO_3, DMF;

For **16**: $BrCH_2CH_2NHCOCF_3$, K_2CO_3, DMF;

For **17**: $BrCH_2CH_2$morpholide, K_2CO_3, DMF.

1,2,4-Benzotriazin-3-amine 1-oxide (**3**) (Scheme 1: R_1 =R_2 =H) was synthesized from nitroaniline using Method A. Diazotisation gave the phenol **18** which was chlorinated to give chloride **19** (Scheme 7). Reaction of chloride **19** with glycine ethyl ester gave the ester **20**. Base catalysed hydrolysis of the ester gave the acid **21**.

Scheme 7



Reagents:

a) $NaNO_2$, HCl;

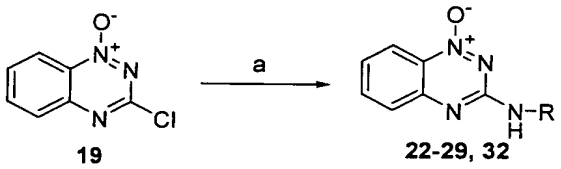
b) $POCl_3$, $PhNMe_2$;

c) $NH_2CH_2CO_2Et$, Et_3N, DME;

d) NaOH, MeOH.

Reaction of chloride **19** with various alkylamines in refluxing DME gave 1-oxides **22-29** and **32** in good yields (Scheme 8).

Scheme 8

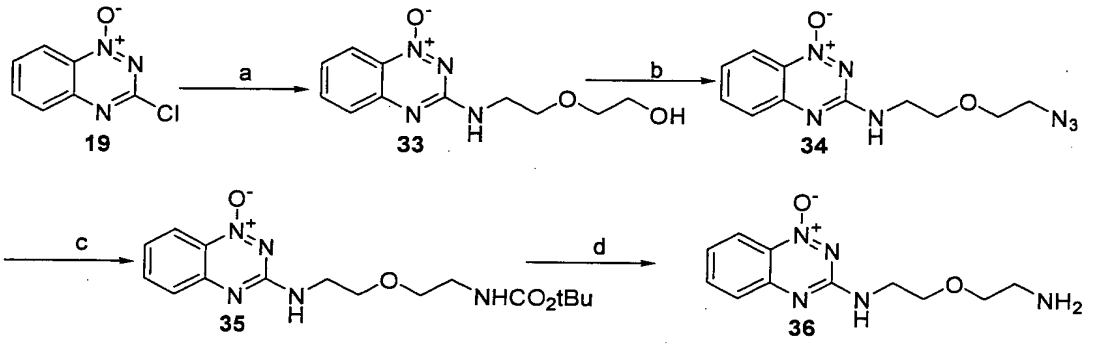


Compound	Reagent	R =
22	$NH_2(CH_2)_2OH$	$-(CH_2)_2OH$
23	$NH_2(CH_2)_2OMe$	$-(CH_2)_2OMe$
24	$NH_2(CH_2)_3OH$	$-(CH_2)_3OH$
25	NH_2CH_2CN	$-CH_2CN$
26	$NH_2(CH_2)_2CN$	$-(CH_2)_2CN$
27	$NH_2(CH_2)_3CN$	$-(CH_2)_3CN$
28	$NH_2(CH_2)_3N_3$	$-(CH_2)_3N_3$
29	$NH_2(CH_2)_3NHCO_2tBu$	$-(CH_2)_3NHCO_2tBu$
32	$NH_2(CH_2)_3N(Et)CO_2tBu$	$-(CH_2)_3N(Et)CO_2tBu$

Reaction of chloride **19** with 2-(aminoethoxy)ethanol gave 1-oxide **33** (Scheme 9) which was converted to the azide **34** by reaction with methanesulfonyl chloride and

displacement with azide. Reduction with propanedithiol gave selective reduction of the azide **34** to an amine which was protected as carbamate **35**. Deprotection of carbamate **35** under acidic conditions gave amine **36**.

Scheme 9



Reagents:

a) $NH_2(CH_2)_2O(CH_2)_2OH$, Et_3N, DCM;

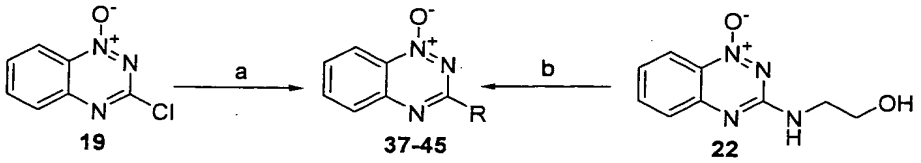
b) MsCl, Et_3N, DCM;

c) $HS(CH_2)_3SH$, Et_3N, MeOH; then di-*t*-butyldicarbonate, THF;

d) HCl, MeOH.

Reaction of chloride **19** with a variety of amines gave 1-oxides **37**, **38**, **40-45** (Scheme 10). Reaction of alcohol **22** with methanesulfonyl chloride and displacement with di-n-propylamine gave 1-oxide **39**.

Scheme 10

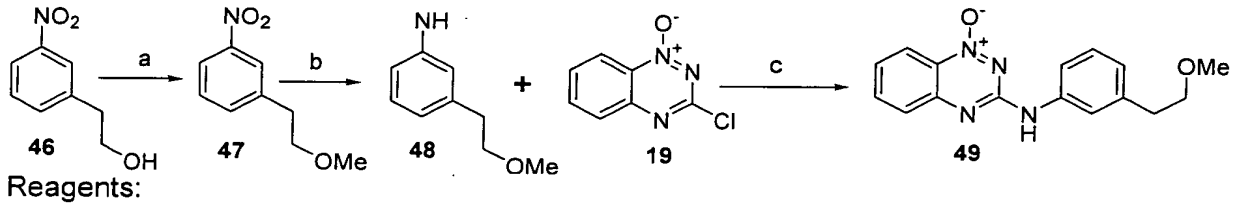


Compound	Reagents	R =
37	$NH_2(CH_2)_2NMe_2$, DME	$-NH(CH_2)_2NMe_2$
38	$NHMe(CH_2)_2NMe_2$, DME	$-NMe(CH_2)_2NMe_2$
39	MsCl, Et_3N, DCM; then $HNPr_2$	$-NH(CH_2)_2NPr_2$
40	$NH_2(CH_2)_2N$-Pyrrolidine, DME	$-NH_2(CH_2)_2N$-Pyrrolidine
41	$NH_2(CH_2)_2N$-Morpholine, DME	$-NH(CH_2)_2N$-Morpholine
42	$NH_2(CH_2)_2N$-piperidine, DME	$-NH(CH_2)_2N$-piperidine
43	$NH_2(CH_2)_2N$-2,6-dimethylpiperidine, DME	$-NH(CH_2)_2N$-2,6-dimethyl-piperidine

44	$NH_2(CH_2)_3NMe_2$, DME	$-NH(CH_2)_3NMe_2$
45	Aniline, HCl, DME	-NHPhenyl

Aniline **48** was prepared by methylation of 3-nitrophenethyl alcohol **46** (Scheme 11) and reduction of the ether **47**. Aniline **48** was coupled to chloride **19** to give 1-oxide **49**.

Scheme 11



Reagents:

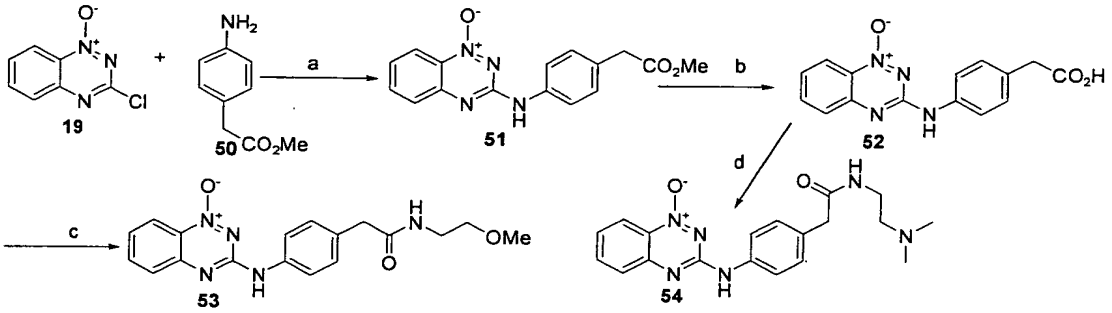
a) NaH, MeI, THF;

b) H_2, Pd/C, EtOH;

c) **19** + **48**, DMSO.

Reaction of chloride **19** and aniline **50** gave ester **51** (Scheme 12). Hydrolysis of the ester **51** gave acid **52** which was condensed with methoxyethylamine and CDI to give amide **53**. Condensation of **52** with N,N-dimethylethanediamine gave **54**.

Scheme 12



Reagents:

a) 19 + 50, DMSO;

b) aqueous NaOH, MeOH;

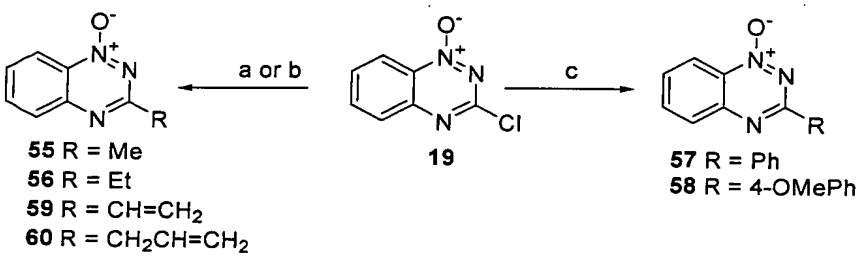
c) CDI, Methoxyethylamine, DMF;

d) CDI, $NH_2CH_2CH_2NMe_2$, DMF.

Stille reaction of chloride **19** with tetramethyltin and $Pd(PPh)_3$ in refluxing DME gave the 3-methyl 1-oxide **55** (Scheme 13). Similarly, reaction of **19** with tetraethyltin gave 3-ethyl 1-oxide **56**, reaction with vinyltributyltin gave 3-vinyl 1-oxide **59**, and reaction with allyltributyltin gave 3-allyl 1-oxide **60**. Suzuki reaction of chloride **19** with

phenylboronic acid and 4-methoxyphenylboronic acid gave 3-aryl derivatives **57** and **58**, respectively.

Scheme 13



Reagents:

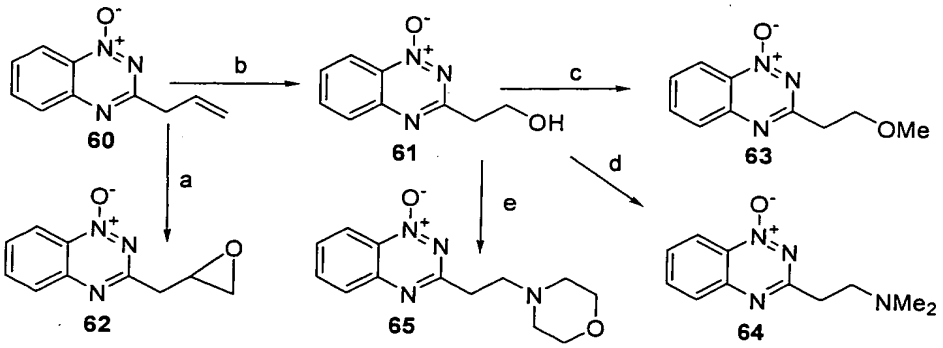
a) R_4Sn, $Pd(PPh_3)_4$, DME;

b) NBu_3SnR, $Pd(PPh_3)_4$, DME;

c) $RB(OH)_2$, $Pd(PPH_3)_4$, DME.

Oxidation of alkene **60** with MCPBA gave epoxide **62** (Scheme 14). Ozonolysis of **60**, followed by a reductive workup gave **61**. Treatment of alcohol **61** with TMS–diazomethane and HBF_4 gave the ether **63**. Treatment of alcohol **61** with methanesulfonyl chloride followed by either dimethylamine or morpholine gave 1-oxides **64** and **65**, respectively.

Scheme 14



Reagents:

a) MCPBA, DCM;

b) O_3, DCM, MeOH; then $NaBH_4$;

c) $TMSCH_2N_2$, HBF_4, DCM;

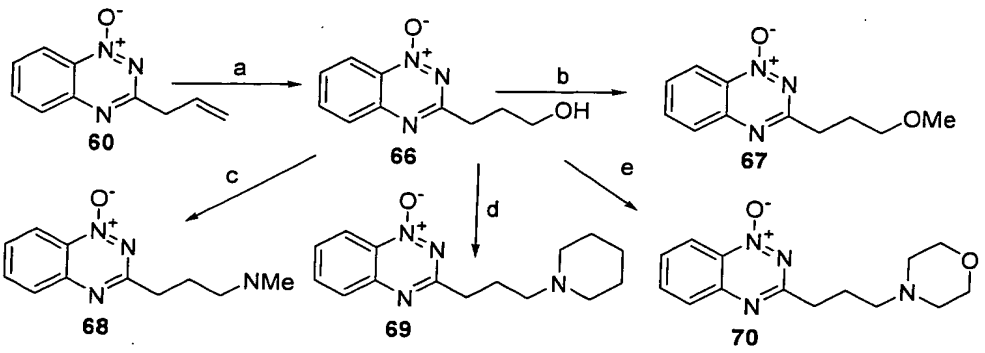
d) MsCl, Et_3N, DCM; then $HNMe_2.HCl$, Et_3N, THF;

e) MsCl, Et_3N, DCM; then morpholine, THF.

Hydroboration and oxidation of alkene **60** gave alcohol **66** which was methylated with TMS-diazomethane and HBF_4 to give ether **67** (Scheme 15). Treatment of alcohol **66**

with methanesulfonyl chloride and displacement with secondary amines gave 1-oxides **68-70**.

Scheme 15



Reagents:

a) 9-BBN, THF; then 30% H_2O_2, NaOH;

b) $TMSCH_2N_2$, HBF_4, DCM;

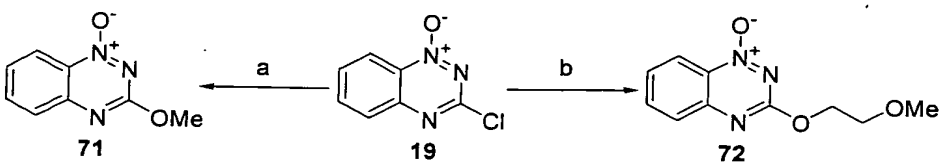
c) MsCl, Et_3N, DCM; then $HNMe_2$, DMF;

d) MsCl, Et_3N, DCM; then piperidine, DMF;

e) MsCl, Et_3N, DCM; then morpholine, DMF.

Reaction of chloride **19** with sodium methoxide gave ether **71** (Scheme 16) and similarly reaction of **19** with sodium 2-methoxyethoxide gave ether **72**.

Scheme 16



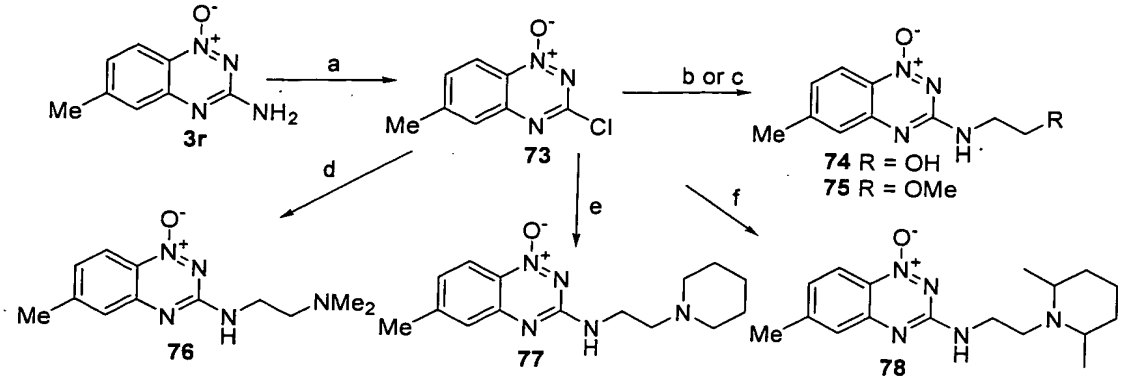
Reagents:

a) Na, MeOH;

b) Na, $MeOCH_2CH_2OH$;

Diazotisation of amine **3r** in trifluoroacetic acid and chlorination of the intermediate phenol gave chloride **73** (Scheme 17). Nucleophilic displacement of chloride **73** with a variety of amines gave the 1-oxides **74-78**.

Scheme 17



Reagents:

a) $NaNO_2$, TFA; then $POCl_3$, DMF;

b) $NH_2CH_2CH_2OH$, DME;

c) $NH_2CH_2CH_2OMe$, DME;

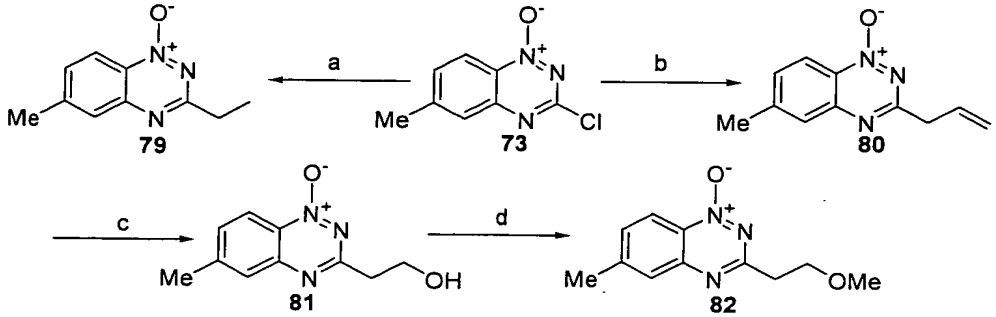
d) $NH_2CH_2CH_2NMe_2$, DME;

e) $NH_2CH_2CH_2N$-piperidine, DME;

f) $NH_2CH_2CH_2N$-2,6-dimethylpiperidine, DME.

Stille reaction of chloride **73** with tetraethyltin and $Pd(PP_3)_4$ gave 1-oxide **79**, while reaction with allyltributyltin under similar conditions gave 1-oxide **80** (Scheme 18). Ozonolysis of **80** with a reductive workup gave alcohol **81** which was methylated with TMS-diazomethane and HBF_4 to give ether **82**.

Scheme 18



Reagents:

a) Et_4Sn, $Pd(PPh_3)_4$, DME;

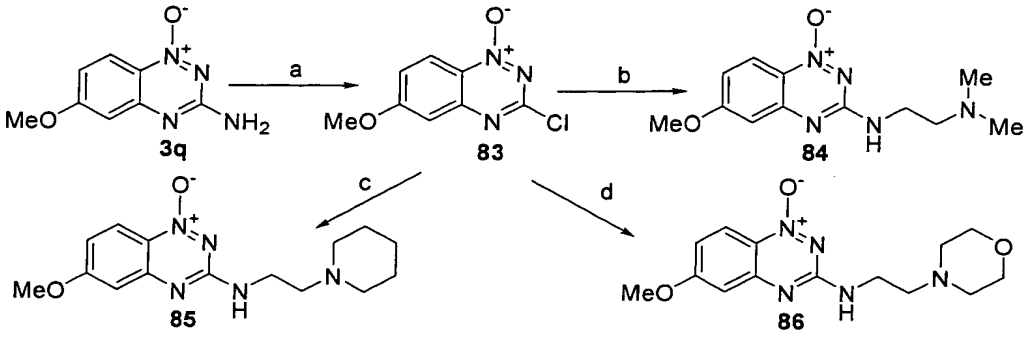
b) $nBu_3Snallyl$, $Pd(PPh_3)_4$, DME;

c) O_3, DCM, MeOH, $NaBH_4$;

d) $TMSCH_2N_2$, HBF_4, DCM.

Diazotisation of amine **3q** in trifluoroacetic acid and chlorination of the intermediate phenol gave chloride **83** (Scheme 19). Nucleophilic displacement of chloride **83** with a variety of amines gave the 1-oxides **84-86**.

Scheme 19



Reagents:

a) $NaNO_2$, TFA; then $POCl_3$, DMF;

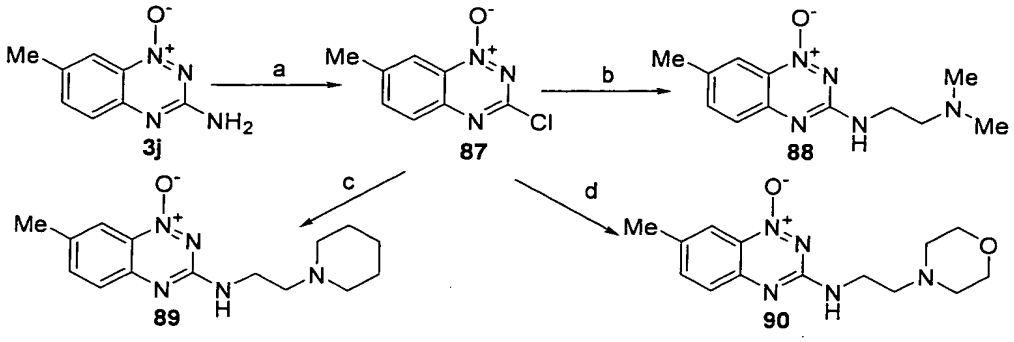
b) $NH_2CH_2CH_2NMe_2$, DME;

c) $NH_2CH_2CH_2N$-piperidine, DME;

d) $NH_2CH_2CH_2N$-morpholine, DME.

Diazotisation of amine **3j** and chlorination of the intermediate phenol gave chloride **87** (Scheme 20). Nucleophilic displacement of chloride **87** with a variety of amines gave the 1-oxides **88-90**.

Scheme 20



Reagents:

a) $NaNO_2$, aq. HCl; then $POCl_3$, DMF;

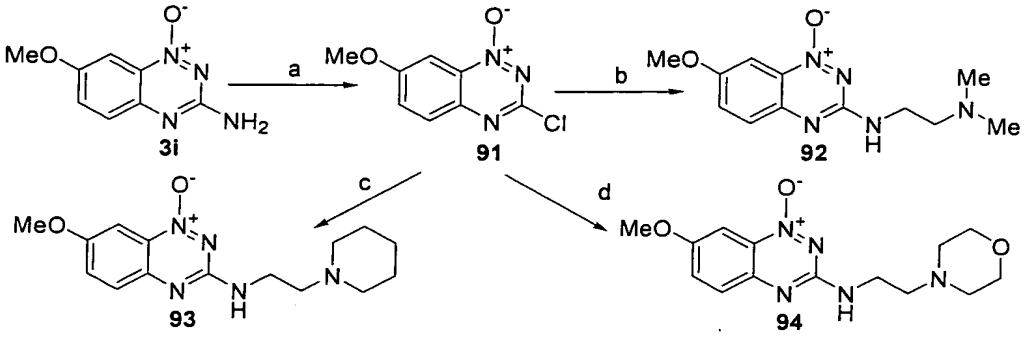
b) $NH_2CH_2CH_2NMe_2$, DME;

c) $NH_2CH_2CH_2N$-piperidine, DME;

d) $NH_2CH_2CH_2N$-morpholine, DME.

Diazotisation of amine **3i** and chlorination of the intermediate phenol gave chloride **91** (Scheme 21). Nucleophilic displacement of chloride **91** with a variety of amines gave the 1-oxides **92-94**.

Scheme 21



Reagents:

a) $NaNO_2$, aq. HCl; then $POCl_3$, DMF;

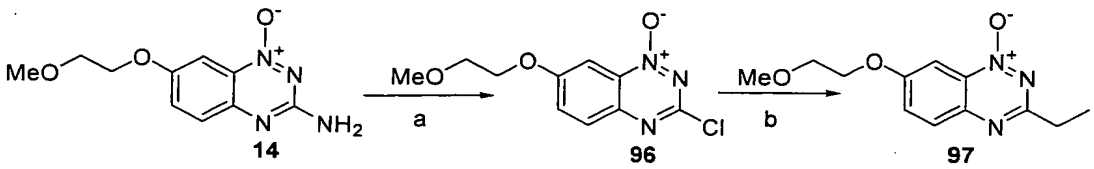
b) $NH_2CH_2CH_2NMe_2$, DME;

c) $NH_2CH_2CH_2N$-piperidine, DME;

d) $NH_2CH_2CH_2N$-morpholine, DME.

Diazotisation of amine **14** and chlorination of the intermediate phenol gave chloride **96** (Scheme 22). Stille reaction of chloride **96** with tetraethyltin and $Pd(PPh_3)_4$ in DMF gave the 1-oxide **97**

Scheme 22



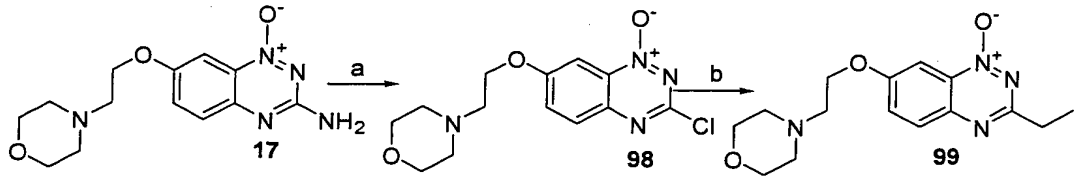
Reagents:

a) $NaNO_2$, aq. HCl; then $POCl_3$, DMF;

b) Et_4Sn, $Pd(PPh_3)_4$, DMF.

Similarly, diazotisation of amine **17** and chlorination of the intermediate phenol gave chloride **98** (Scheme 23). Stille reaction of chloride **98** with tetraethyltin and $Pd(PPh_3)_4$ in DMF gave the 1-oxide **99**.

Sch me 23



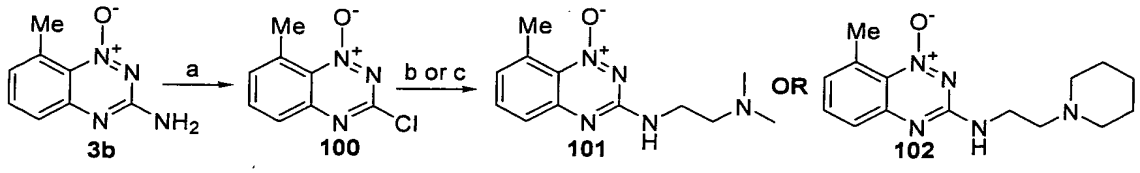
Reagents:

c) $NaNO_2$, aq. HCl; then $POCl_3$, DMF;

d) Et_4Sn, $Pd(PPh_3)_4$, DMF.

Diazotisation of amine **3b** and chlorination of the intermediate phenol gave chloride **100** (Scheme 24). Nucleophilic displacement with amines gave 1-oxides **101** and **102**.

Scheme 24



Reagents:

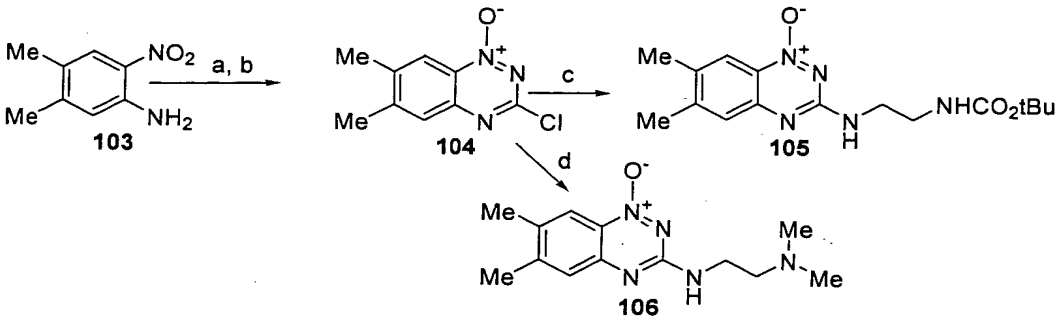
a) $NaNO_2$, TFA; then $POCl_3$, DMF;

b) $NHMe(CH_2)_2NMe_2$, DME;

c) $NH_2(CH_2)_2$N-piperidine, DME.

Reaction of nitroaniline **103** with cyanamide and condensation of the intermediate guanidine under basic conditions, followed by diazotisation and chlorination gave chloride **104** (Scheme 25). Displacement of **104** with amines gave 1-oxides **105** and **106**.

Scheme 25



Reagents:

a) NH_2CN, HCl; then NaOH;

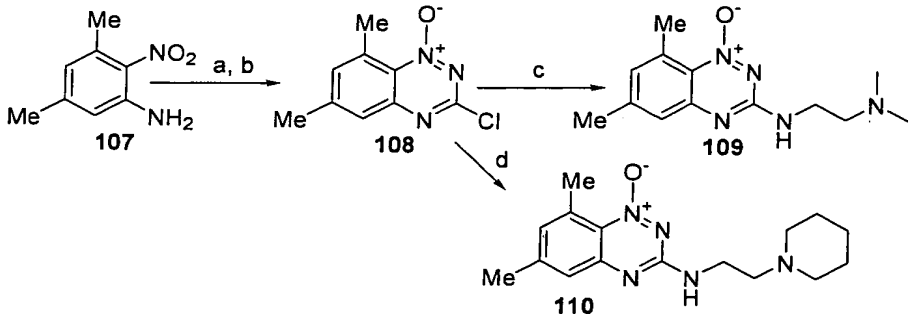
b) $NaNO_2$, TFA; then $POCl_3$, DMF;

c) $NH_2CH_2CH_2N(Et)CO_2tBu$, DME;

d) $NHMe(CH_2)_2NMe_2$, DME.

Reaction of nitroaniline **107** with cyanamide and condensation of the intermediate guanidine under basic conditions, followed by diazotisation and chlorination gave chloride **108** (Scheme 26). Displacement of **108** with amines gave 1-oxides **109** and **110**.

Scheme 26



Reagents:

a) NH_2CN, HCl; then NaOH;

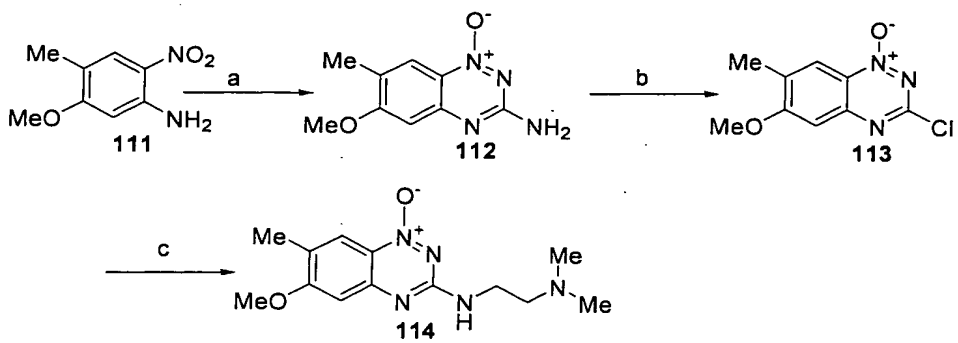
b) $NaNO_2$, TFA; then $POCl_3$, DMF;

c) $NH_2CH_2CH_2NMe_2$, DME;

d) $NHMe(CH_2)_2N$piperidine, DME.

Reaction of nitroaniline **111** with cyanamide and condensation of the intermediate guanidine under basic conditions gave amine **112** (Scheme 27). Diazotisation and chlorination of **112** gave chloride **113**. Displacement of **113** with *N,N*-dimethylethylenediamine gave 1-oxide **114**.

Scheme 27



Reagents:

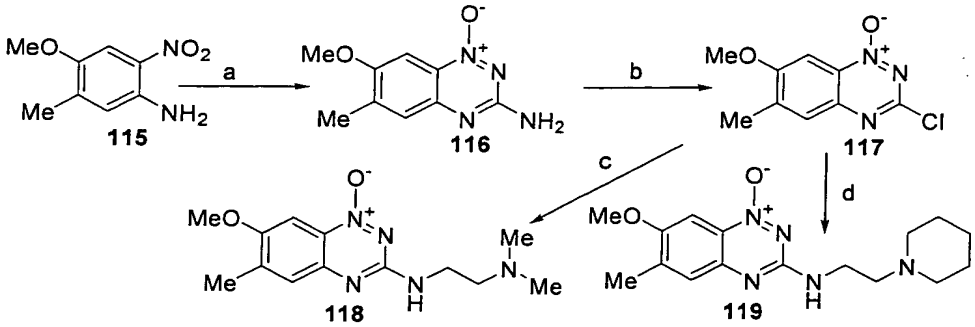
a) NH_2CN, HCl; then NaOH;

b) $NaNO_2$, TFA; then $POCl_3$, DMF;

c) $NH_2CH_2CH_2NMe_2$, DME.

Reaction of nitroaniline **115** with cyanamide and condensation of the intermediate guanidine under basic conditions gave amine **116** (Scheme 28). Diazotisation and chlorination of **116** gave chloride **117**. Displacement of **117** with dimethylethylenediamine gave 1-oxide **118**, while reaction of **117** with 2-(1-piperidinyl)ethylamine gave 1-oxide **119**.

Scheme 28



Reagents:

a) NH_2CN, HCl; then NaOH;

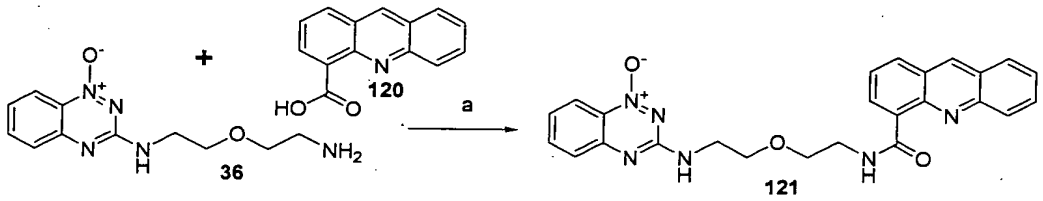
b) $NaNO_2$, TFA; then $POCl_3$, DMF;

c) $NH_2CH_2CH_2NMe_2$, DME;

d) $NH_2CH_2CH_2N$piperidine, DME.

The imidazolide of **120** was formed using CDI in DMF and was coupled to amine **36** to give 1-oxide **121** (Scheme 29).

Scheme 29

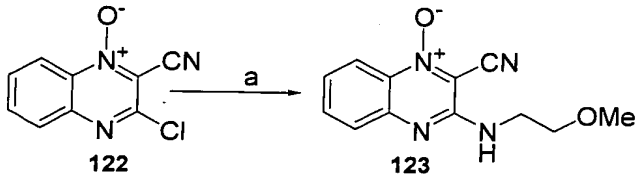


Reagents:

a) **120**, CDI, DMF; then **36**.

Reaction of the chloride **122** with methoxyethylamine gave 1-oxide **123** (Scheme 30).

Scheme 30

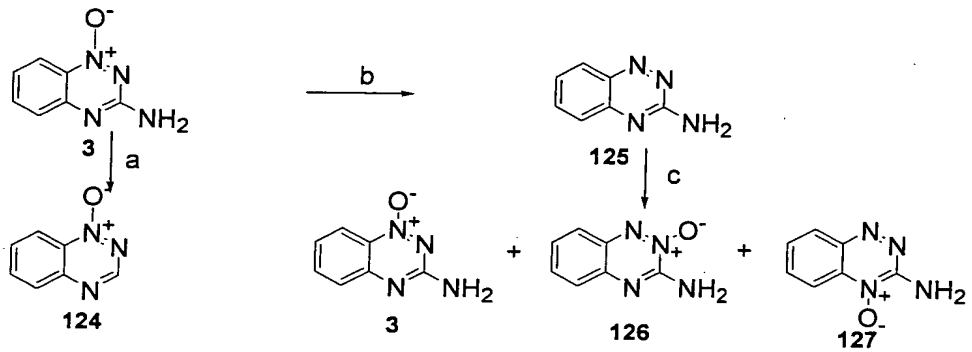


Reagents:

a) $MeOCH_2CH_2NH_2$, DME.

Amine **3** was deaminated with isoamyl nitrite in DMF to give 1-oxide **124** (Scheme 31). Reduction of amine **3** with sodium dithionite in aqueous ethanol gave benzotriazine **125** which was oxidised with MCPBA to 1-oxide **3**, 2-oxide **126**, and 4-oxide **127**.

Scheme 31



Reagents:

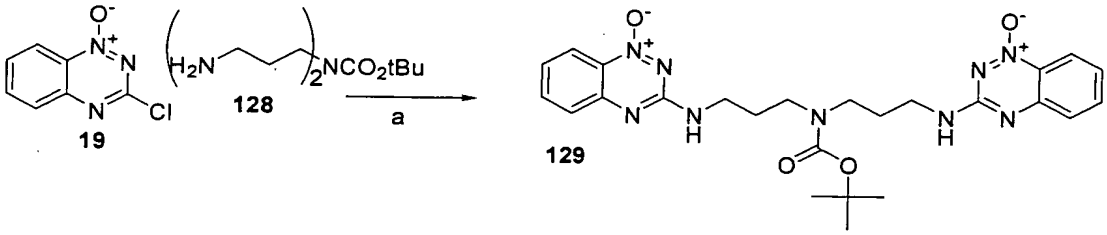
a) Isoamylnitrite, DMF;

b) $Na_2S_2O_4$, 70% EtOH;

c) MCPBA, DCM.

Reaction of chloride **19** with diamine **128** gave bis-1-oxide **129** (Scheme 32).

Scheme 32

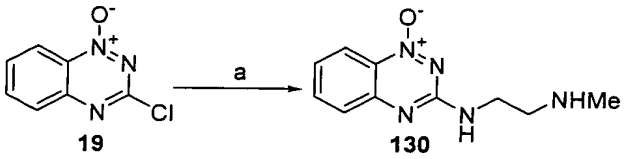


Reagents:

a) **19** + **128**, Et_3N, DCM.

Reaction of chloride **19** with *N*-methylethylenediamine gave 1-oxide **130** (Scheme 33).

Scheme 33



Reagents:
a) $NH_2CH_2CH_2NHMe$, Et_3N, DCM.

Examples of the compounds of the invention

The following examples are representative of the invention and the detailed methods for preparing them, however, the scope of the invention is not to be taken as being limited to these examples.

Analyses were carried out in the Microchemical Laboratory, University of Otago, Dunedin, NZ. Melting points were determined on an Electrothermal 2300 Melting Point Apparatus. NMR spectra were obtained on a Bruker AM-400 spectrometer at 400 MHz for ^1H and 100 MHz for ^{13}C spectra. Spectra were obtained in $CDCl_3$ unless otherwise specified, and are referenced to Me_4Si. Chemical shifts and coupling constants were recorded in units of ppm and Hz, respectively. Assignments were determined using COSY, HSQC, and HMBC two-dimensional experiments. Mass spectra were determined on a VG-70SE mass spectrometer using an ionizing potential of 70 eV at a nominal resolution of 1000. High-resolution spectra were obtained at nominal resolutions of 3000, 5000, or 10000 as appropriate. All spectra were obtained as electron impact (EI) using PFK as the reference unless otherwise stated. Solutions in organic solvents were dried with anhydrous Na_2SO_4. Solvents were evaporated under reduced pressure on a rotary evaporator. Thin-layer chromatography was carried out on aluminum-backed silica gel plates (Merck 60 F_{254}) with visualization of components by UV light (254 nm) or exposure to I_2. Column chromatography was carried out on silica gel, (Merck 230-400 mesh). All compounds designated for biological testing were analysed at >99% purity by reverse phase HPLC using a Philips PU4100 liquid chromatograph, a Phenomenex BondClone 10-C18 stainless steel column (300mm x 3.9 mm i.d.) and a Philips PU4120 diode array detector. Chromatograms were run using various gradients of aqueous (1 M NaH_2PO_4, 0.75 M heptanesulfonic acid, 0.5 M dibutylammonium phosphate, and MilliQ water in a 1:1:1:97 ratio) and organic (80%

MeOH/MilliQ water) phases. DCM refers to dichloromethane; DME refers to dimethoxyethane, DMF refers to dry dimethylformamide; ether refers to diethyl ether; EtOAc refers to ethyl acetate; EtOH refers to ethanol; MeOH refers to methanol; pet. ether refers to petroleum ether, boiling range 40-60 °C; THF refers to tetrahydrofuran dried over sodium benzophenone ketyl. All solvents were freshly distilled.

Example 1

Method A: Condensation of 2-nitroanilines (1) with cyanamide. 2-Nitroaniline (**1**) (4.3 mmol) and cyanamide (22 mmol) were melted together at 100 °C, cooled to ca. 50 °C, and cHCl (5 mL) added carefully. The mixture was stirred until the exotherm subsided then stirred at 100 °C for 2 h. If necessary, more cyanamide (22 mmol) was added and the mixture stirred at 100 °C for 4 h. The mixture was cooled to 20 °C, made strongly basic with 7.5 M NaOH solution (ca. 50 mL) and the mixture heated at 100 °C for 1 h then cooled to 20 °C and diluted with water (100 mL). The precipitate was filtered, washed with water (2 × 10 mL), ether (2 × 10 mL) and dried. If necessary, the solid was chromatographed, eluting with a gradient (2-5%) of MeOH/$CHCl_3$, to give the corresponding 1,2,4-benzotriazin-3-amine 1-oxide (**3**).

Example 2

Method B: Condensation of 2-nitrohalobenzenes (2) with guanidine. Guanidine hydrochloride (104 mmol) was added to a stirred solution of KOtBu (104 mmol) in abs. EtOH (80 mL) and the mixture stirred at 20 °C for 1 h. The mixture was filtered, and the filtrate added slowly to a stirred solution of 2-nitrohalobenzene (**2**) (26 mmol) in absolute EtOH (50 mL). The mixture was heated at reflux temperature for 72 h then cooled, acidified with cHCl and the solvent evaporated. The residue was suspended in 0.5 M HCl and the precipitate was filtered. The aqueous fraction was washed with $CHCl_3$, basified with aqueous NH_3, and extracted into EtOAc. The organic fraction was dried and the solvent evaporated. The residue was suspended in 10% aq. NaOH and heated at 100 °C for 2 h. The precipitate was filtered, washed with water (2 × 10 mL), ether (2 × 10 mL) and dried. If necessary, the solid was chromatographed, eluting with a gradient (2-5%) of MeOH/$CHCl_3$, to give the corresponding 1,2,4-benzotriazin-3-amine 1-oxide (**3**).

Example 3

8-Methoxy-1,2,4-benzotriazin-3-amine 1-oxide (3a). Method A using 3-methoxy-2-nitroaniline (**1a**) (Shigyo et. al., *Chem. Pharm. Bull.* **1993**, *41*, 1573) gave **3a** (51%)

as a yellow powder, mp (H_2O) 235-239 °C; ^1H NMR [$(CD_3)_2SO$] δ 7.62 (dd, *J* = 8.3, 8.0 Hz, 1 H, H-6), 7.15 (br s, 2 H, NH_2), 7.02 (d, *J* = 8.3 Hz, 1 H, H-7), 6.80 (d, *J* = 8.0 Hz, 1 H, H-5), 3.83 (s, 3 H, OCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 160.0, 153.3, 151.4, 135.4, 122.6, 117.0, 105.1, 56.4; Anal. calc. for $C_8H_8N_4O_2$: C, 50.0; H, 4.2; N, 29.2; found C, 50.3; H, 4.1; N, 29.2%.

Example 4

8-Methyl-1,2,4-benzotriazin-3-amine 1-oxide (3b). Method A using 3-methyl-2-nitroaniline (**1b**) gave **3b** (100%) as a yellow powder, mp (DMF) 265 °C (dec.); ^1H NMR [$(CD_3)_2SO$] δ 7.59 (dd, *J* = 8.3, 7.3 Hz, 1 H, H-6), 7.35 (d, *J* = 8.0 Hz, 1 H, H-5), 7.18 (s, 2 H, NH_2), 7.10 (dd, *J* = 7.2, 0.8 Hz, 1 H, H-7), 2.79 (s, 3 H, CH_3); Anal. calc. for $C_8H_8N_4O$: C, 54.5; H, 4.6; N, 31.8; found C, 54.6; H, 4.7; N, 31.9%.

Example 5

8-Fluoro-1,2,4-benzotriazin-3-amine 1-oxide (3c). Method B using 2,6-difluoroaniline (**2c**) gave **3c** (49%) as a yellow powder, mp (DCM/pet. ether) 270-278 °C (dec.) [lit. (Suzuki & Kawakami, *Synthesis* **1977**, 855) mp 271 °C (dec.)]; ^1H NMR [$(CD_3)_2SO$] δ 7.69 (ddd, *J* = 10.9, 8.3, 5.2 Hz, 1 H, H-6), 7.45 (br s, 2 H, NH_2), 7.31 (dd, *J* = 9.6, 1.0 Hz, 1 H, H-5), 7.09 (ddd, *J* = 12.0, 8.0, 1.0 Hz, 1 H, H-7); ^{13}C NMR [$(CD_3)_2SO$] δ 160.2 (d, *J* = 5.3 Hz), 153.5 (d, *J* = 264.3 Hz), 151.1 (d, *J* = 3.2 Hz), 135.2 (d, *J* = 4.4 Hz), 121.7 (d, *J* = 4.5 Hz), 121.1, 110.0 (d, *J* = 20.8 Hz); HRMS (EI^+) calc. for $C_7H_5FN_4O$ (M^+) *m/z* 180.0360, found 180.0441.

Example 6

8-Chloro-1,2,4-benzotriazin-3-amine 1-oxide (3d). Method A using 3-chloro-2-nitroaniline (**1d**) gave **3d** (30%) as a yellow powder, mp (DMF) 280-290 °C (dec.); ^1H NMR [$(CD_3)_2SO$] δ 7.63 (dd, *J* = 8.4, 7.8 Hz, 1 H, H-6), 7.45 (dd, *J* = 8.6, 1.0 Hz, 1 H, H-7), 7.42 (br s, 2 H, NH_2), 7.36 (dd, *J* = 7.6, 1.1 Hz, 1 H, H-5); HRMS (EI) calc. for $C_7H_5N_4O^{35}Cl$ (M^+) *m/z* 196.0152, found 196.0152; calc for $C_7H_5N_4O^{37}Cl$ (M^+) *m/z* 198.0122, found 198.0124.

Example 7

8-Trifluoromethyl-1,2,4-benzotriazin-3-amine 1-oxide (3e). Method A using 3-trifluoromethyl-2-nitroaniline (**1e**) gave **3e** (14%) as a yellow powder, mp (DCM/pet. ether) 280-286 °C (dec.); ^1H NMR [$(CD_3)_2SO$] δ 7.78-7.87 (m, 3 H, H-5, H-6, H-7),

7.55 (br s, 2 H, NH_2); Anal. calc. for $C_8H_5F_3N_4O$: C, 41.8; H, 2.2; N, 24.3; F, 24.8; found C, 41.6; H, 2.1; N, 24.3; F, 24.9%.

Example 8

8-(Methylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide (3f).

3-(Methylsulfanyl)-2-nitroaniline (1f). A solution of LiSMe (1.19 g, 22.0 mmol) in DMF (20 mL) was added dropwise to a stirred solution of 3-chloro-2-nitroaniline (**1d**) (3.17 g, 18.4 mmol) in DMF (80 mL) at 20 °C and the mixture stirred for 2 h. The mixture was poured into water (300 mL) and extracted with EtOAc (2 × 150 mL). The combined organic fraction was washed with water (2 × 100 mL), brine (50 mL), dried, and the solvent evaporated. The residue was chromatographed, eluting with 20% EtOAc/pet. ether, to give (i) starting material (0.51 g, 16%) and (ii) sulfide (**1f**) (2.36 g, 70%) as red crystals, mp (EtOAc/pet. ether) 70-72 °C; ^{1}H NMR δ 7.21 (t, *J* = 8.2 Hz, 1 H, H-5), 6.55 (d, *J* = 8.2 Hz, 2 H, H-4, H-6), 5.92 (br s, 2 H, NH_2), 2.42 (s, 3 H, SCH_3); ^{13}C NMR δ 146.0, 141.6, 133.3, 131.0, 113.9 (2), 17.0; Anal. calc. for $C_7H_8N_2O_2S$: C, 45.6; H, 4.4; N, 15.2; found C, 45.8; H, 4.4; N, 15.1%.

8-(Methylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide (3f). Method A using **1f** gave **3f** (68%) as a yellow powder, mp (H_2O) 271-275 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.63 (dd, *J* = 8.3, 8.0 Hz, 1 H, H-6), 7.28 (s, 2 H, NH_2), 7.17 (d, *J* = 8.3 Hz, 1 H, H-5), 6.98 (d, *J* = 8.0 Hz, 1 H, H-7), 2.39 (s, 3 H, SCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 159.9, 151.1, 137.1, 134.7, 127.9, 120.1, 118.7, 15.7; Anal. calc. for $C_8H_8N_4OS$: C, 46.1; H, 3.9; N, 26.9; found C, 45.9; H, 3.9; N, 26.7%.

Example 9

8-(Butylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide (3g).

3-(Butylsulfanyl)-2-nitroaniline (1g). A solution of LiSBu (1.39 g, 14.5 mmol) in DMF (10 mL) was added dropwise to a stirred solution of 3-chloro-2-nitroaniline (**1d**) (2.08 g, 12.05 mmol) in DMF (50 mL) at 20 °C and the mixture stirred for 2 h. The mixture was poured into water (300 mL) and extracted with EtOAc (2 × 150 mL). The combined organic fraction was washed with water (2 × 100 mL), brine (50 mL), dried, and the solvent evaporated. The residue was chromatographed, eluting with 20% EtOAc/pet. ether, to give sulfide **1g** (2.47 g, 91%) as a red oil, ^{1}H NMR δ 7.17 (dd, *J* = 8.2, 8.0 Hz, 1 H, H-5), 6.62 (d, *J* = 8.0 Hz, 1 H, H-4), 6.54 (dd, *J* = 8.2, 1.0 Hz, 1 H, H-6), 5.74 (br s, 2 H, NH_2), 2.87 (t, *J* = 7.4 Hz, 2 H, CH_2S), 1.64-1.72 (m, 2 H, CH_2), 1.45-1.53 (m, 2 H, CH_2), 0.95 (s, 3 H, CH_3); ^{13}C NMR δ 145.3, 140.1, 133.0, 132.4,

115.0, 113.9, 33.0, 29.8, 22.2, 13.6; MS (EI) *m/z* 226 (M^+, 35%), 106 (100); HRMS (EI) calc. for $C_{10}H_{14}N_2O_2S$ (M^+) *m/z* 226.0776, found 226.0773.

8-(Butylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide (3g). Method A using **1g** gave **4i** (26%) as a red/brown solid, mp (MeOH/$CHCl_3$) 233-236 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.61 (dd, *J* = 8.2, 7.4 Hz, 1 H, H-6), 7.27 (s, 2 H, NH_2), 7.16 (dd, *J* = 8.2, 0.8 Hz, 1 H, H-5), 7.04 (dd, *J* = 7.4, 0.8 Hz, 1 H, H-7), 2.86 (t, *J* = 7.3 Hz, 2 H, CH_2S), 1.62-1.70 (m, 2 H, CH_2), 1.44-1.52 (m, 2 H, CH_2), 0.93 (s, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 159.8, 151.1, 136.4, 134.7, 128.0, 120.1, 119.1, 31.0, 28.8, 21.7, 13.5; Anal. calc. for $C_{11}H_{14}N_4OS$: C, 52.8; H, 5.6; N, 22.4; found C, 52.7; H, 5.6; N, 22.6%.

Example 10

3-Amino-1,2,4-benzotriazin-7-ol 1-oxide (3h). Method A using 4-amino-3-nitrophenol (**1h**) gave **3h** (97%) as a yellow powder, mp > 300 °C [lit. (Friebe et. al., *US Patent* 5,856,325, Jan 5, 1999) mp (HOAc) >270 °C]; ^{1}H NMR [$(CD_3)_2SO$] δ 10.37 (br s, 1 H, OH), 7.48 (dd, *J* = 7.7, 2.6 Hz, 1 H, H-6), 7.40-7.37 (m, 2 H, H-5, H-8), 6.96 (br s, 2 H, NH_2).

Example 11

3-Amino-1,2,4-benzotriazin-7-ol 1-oxide (3h). Method A using 4-hydroxy-2-nitroaniline (**1i**) gave **3i** (93%) as a yellow powder, mp (HOAc) 269-271 °C [lit. (Mason & Tennant, *J. Chem. Soc. (B)* **1970**, 911) mp (HOAc) 271 °C]; ^{1}H NMR [$(CD_3)_2SO$] δ 7.48-7.53 (m, 3 H, H-5, H-6, H-8), 7.10 (br s, 2 H, NH_2), 3.88 (s, 3 H, OCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 159.3, 156.3, 144.9, 129.7, 128.3, 127.3, 97.9, 55.8.

Example 12

7-Methyl-1,2,4-benzotriazin-3-amine 1-oxide (3j). Method A using 4-methyl-2-nitroaniline (**1j**) gave **3j** (74%) as a yellow powder, mp (DMF) 270 °C (dec.) [lit. (Pazdera & Potacek, *Chem. Papers* **1988**, *42*, 527) mp (Methylcellosolve) 282 °C]; ^{1}H NMR [$(CD_3)_2SO$] δ 7.94 (s, 1 H, H-8); 7.64 (dd, *J* = 8.7, 1.9 Hz, 1 H, H-6), 7.46 (d, *J* = 8.6 Hz, 1 H, H-5), 7.21 (s, 2 H, NH_2), 2.42 (s, 3 H, CH_3); Anal. calc. for $C_8H_8N_4O$: C, 54.5; H, 4.6; N, 31.8; found C, 54.8; H, 4.5; N, 31.9%.

Example 13

7-Fluoro-1,2,4-benzotriazin-3-amin 1-oxide (3k). Method A using 4-fluoro-2-nitroaniline (**1k**) gave **3k** (78%) as a yellow powder, mp (DMF) 280-290 °C (dec.) [lit.

(Suzuki & Kawakami, *Synthesis* **1977**, 855) mp 290 °C (dec.)]; ^{1}H NMR [$(CD_3)_2SO$] δ 7.89 (dd, *J* = 8.6, 2.9 Hz, 1 H, H-8), 7.76 (ddd, *J* = 9.3, 8.8, 2.9 Hz, 1 H, H-6), 7.62 (dd, *J* = 9.3, 5.2 Hz, 1 H, H-5), 7.35 (br s, 2 H, NH_2); Anal. calc. for $C_7H_5FN_4O$: C, 46.7; H, 2.8; N, 31.1; F, 10.6; found C, 46.7; H, 2.7; N, 31.1; F, 10.7%.

Example 14

7-Chloro-1,2,4-benzotriazin-3-amine 1-oxide (3l). Method A using 4-chloro-2-nitroaniline (**1l**) gave **3l** (39%) as a yellow powder, mp (DCM/pet. ether) 309 °C (dec.) [lit. (Pazdera & Potacek, *Chem. Papers* **1988**, *42*, 527) mp (HOAc) 306-308 °C]; ^{1}H NMR [$(CD_3)_2SO$] δ 8.14 (d, *J* = 1.7 Hz, 1 H, H-8), 7.80 (dd, *J* = 8.8, 1.9 Hz, 1 H, H-6), 7.56 (d, *J* = 9.0 Hz, 1 H, H-5), 7.48 (br s, 2 H, NH_2).

Example 15

7-Trifluoromethyl-1,2,4-benzotriazin-3-amine 1-oxide (3m). Method B using 1-chloro-2-nitro-4-(trifluoromethyl)benzene (**2m**) gave **3m** (30%) as a yellow powder, mp (DCM/pet. ether) 290 °C (dec.) [lit. (Suzuki & Kawakami, *Synthesis* **1977**, 855) mp (acetone/toluene) 301-302 °C]; ^{1}H NMR [$(CD_3)_2SO$] δ 8.38 (br s, 1 H, H-8), 8.01 (dd, *J* = 8.9, 2.0 Hz, 1 H, H-6), 7.72 (br s, 2 H, NH_2), 7.68 (d, *J* = 8.9 Hz, 1 H, H-5); ^{13}C NMR [$(CD_3)_2SO$] δ 161.1, 150.6, 130.7 (*J* = 2.9 Hz), 129.3, 127.5, 123.4 (q, *J* = 272.0 Hz), 123.6 (q, *J* = 32.1 Hz), 118.0 (q, *J* = 10.9 Hz).

Example 16

7-(Methylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide (3n).

4-(Methylsulfanyl)-2-nitroaniline (1n) and 6-(methylsulfanyl)-2-nitroaniline (1ad). *O*-(3-Nitrophenyl)dimethylthiocarbamate (Newman & Karnes, *J. Org. Chem.* **1966**, *31*, 3980) (**4**) (14.05 g, 62.1 mmol) was heated at 235-240 °C for 3 h under N_2, cooled to 20 °C to give crude *S*-(3-nitrophenyl)dimethylthiocarbamate (**5**) which was heated at reflux temperature with KOH solution (7.5 M, 410 mL, 3.1 mol) and MeOH (200 mL) for 2 h. The mixture was cooled to 20 °C and Me_2SO_4 (59 mL, 0.62 mol) added dropwise and the mixture stirred at 20 °C for 16 h. The mixture was partitioned between EtOAc (300 mL) and water (300 mL), the organic fraction washed with water (3 × 100 mL), brine (100 mL), dried, and the solvent evaporated. The residue was chromatographed, eluting with 10% EtOAc/pet. ether, to give 1-(methylsulfanyl)-3-nitrobenzene (**6**) (9.6 g, 91%) as a soft solid, ^{1}H NMR δ 8.05 (dd, *J* = 2.0, 1.9 Hz, 1 H, H-2), 7.96 (dd, *J* = 8.2, 2.0, 0.9 Hz, 1 H, H-4), 7.53 (ddd, *J* = 7.9, 1.9, 1.0 Hz, 1 H, H-

6), 7.43 (dd, J = 8.2, 7.9 Hz, 1 H, H-5), 2.56 (s, 3 H, SCH_3); ^{13}C NMR δ 148.6, 141.6, 131.9, 129.4, 120.3, 119.6, 15.4.

A solution of $NH_2OMe.HCl$ (2.83 g, 34.0 mmol) and nitrobenzene **6** (4.79 g, 28.3 mmol) in DMF (100 mL) was added dropwise to a stirred mixture of KOtBu (13.0 g, 116.6 mmol) and CuCl (0.28 g, 2.83 mmol) in DMF (50 mL) at 5 °C. The mixture was stirred at 20 °C for 3 h, quenched with saturated aqueous NH_4Cl solution (100 mL). The mixture was extracted with EtOAc (3 × 100 mL), the combined organic fraction dried, and the solvent evaporated. The residue was chromatographed, eluting with 10% EtOAc/pet. ether, to give (i) 6-(methylsulfanyl)-2-nitroaniline (**1ad**) (2.11 g, 40%) as a red oil, ^1H NMR δ 8.11 (dd, J = 8.7, 1.5 Hz, 1 H, H-3), 7.66 (dd, J = 7.4, 1.5 Hz, 1 H, H-5), 6.92 (br s, 2 H, NH_2), 6.66 (dd, J = 8.7, 7.4 Hz, 1 H, H-4), 2.38 (s, 3 H, SCH_3); ^{13}C NMR δ 145.0, 140.7, 132.5, 126.6, 124.5, 115.9, 18.2; MS (EI) *m/z* 184 (100, M^+), 169 (10), 150 (30); HRMS calc. for $C_7H_8N_2O_2S$ (M^+) *m/z* 184.0307, found 184.0304; (ii) 4-(methylsulfanyl)-2-nitroaniline (**1n**) (0.8 g, 15%) as a red oil, ^1H NMR δ 8.05 (d, J = 2.3 Hz, 1 H, H-3), 7.34 (dd, J = 8.7, 2.3 Hz, 1 H, H-5), 6.76 (d, J = 8.7 Hz, 1 H, H-6), 6.05 (br s, 2 H, NH_2), 2.46 (s, 3 H, SCH_3); ^{13}C NMR δ 143.1, 136.8, 132.2, 125.8, 125.1, 119.5, 18.0.

7-(Methylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide (3n). Method A using **1n** gave **3n** (56%) as a red solid, mp ($MeOH/CHCl_3$) 245-247 °C; ^1H NMR [$(CD_3)_2SO$] δ 7.79 (d, J = 2.1 Hz, 1 H, H-8), 7.67 (dd, J = 8.9, 2.1 Hz, 1 H, H-6), 7.47 (d, J = 8.9 Hz, 1 H, H-5), 7.28 (s, 2 H, NH_2), 2.58 (s, 3 H, SCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 159.9, 147.0, 135.7, 134.6, 130.1, 126.5, 113.4, 14.6; Anal. calc. for $C_8H_8N_4OS$: C, 46.1; H, 3.9; N, 26.9; found C, 46.1; H, 3.8; N, 26.6%.

Example 17

7-(Butylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide (3o).

4-(Butylsulfanyl)-2-nitroaniline (1o) and 6-(butylsulfanyl)-2-nitroaniline (9). A mixture of crude **5** (7.0 g, 31 mmol) and KOH (7.5 M, 41 mL, 310 mmol) in MeOH (200 mL) was heated at reflux temperature for 2 h. The mixture was cooled to 5 °C and the pH adjusted to 2 with cHCl. The precipitate was collected, washed with water (20 mL), dissolved in EtOAc (200 mL), dried, and the solvent evaporated. The residue was dissolved in DMF (100 mL) and K_2CO_3 (5.15 g, 37.3 mmol) added and the mixture stirred at 20 °C for 30 min. n-Butylbromide (4.0 mL, 37.3 mmol) was added and the mixture stirred at 80 °C for 16 h. The mixture was cooled and the solvent evaporated. The residue was partitioned between EtOAc (300 mL) and water

(300 mL), the organic fraction washed with water (2 × 100 mL), brine (100 mL), dried, and the solvent evaporated. The residue was chromatographed, eluting with 10% EtOAc/pet. ether, to give 3-(butylsulfanyl)nitrobenzene (**7**) (5.53 g, 84%) as a yellow oil, ^{1}H NMR δ 8.10 (dd, *J* = 2.0, 2.0 Hz, 1 H, H-2), 7.97 (ddd, *J* = 8.1, 2.0, 0.9 Hz, 1 H, H-4), 7.57 (ddd, *J* = 8.1, 2.0, 0.9 Hz, 1 H, H-6), 7.42 (dd, *J* = 8.1, 8.1 Hz, 1 H, H-5), 3.01 (dd, *J* = 7.4, 7.3 Hz, 2 H, CH_2S), 1.64-1.71 (m, 2 H, CH_2), 1.43-1.53 (m, 2 H, CH_2), 0.95 (t, *J* = 7.3 Hz, 3 H, CH_3); ^{13}C NMR δ 148.6, 140.5, 133.5, 129.4, 121.9, 120.1, 32.6, 30.7, 21.9, 13.6; MS (EI) *m/z* 211 (M^+, 60%), 155 (100); HRMS (EI) calc. for $C_{10}H_{13}NO_2S$ (M^+) *m/z* 211.0667, found 211.0661.

A solution of $NH_2OMe.HCl$ (2.61 g, 31.2 mmol) and **7** (5.5 g, 26.0 mmol) in DMF (40 mL) was added dropwise to a stirred mixture of KOtBu (12.0 g, 106.7 mmol) and CuCl (0.26 g, 2.6 mmol) in DMF (50 mL) at 5 °C. The mixture was stirred at 20 °C for 6 h, quenched with saturated aqueous NH_4Cl solution (300 mL). The mixture was extracted with EtOAc (3 × 100 mL), the combined organic fraction dried, and the solvent evaporated. The residue was chromatographed, eluting with 5% EtOAc/pet ether, to give (i) 6-(butylsulfanyl)-2-nitroaniline (**9**) (2.34 g, 40%) as a red oil, ^{1}H NMR δ 8.12 (dd, *J* = 8.7, 1.5 Hz, 1 H, H-3), 7.66 (dd, *J* = 7.3, 1.5 Hz, 1 H, H-5), 7.00 (br s, 2 H, NH_2), 6.64 (dd, *J* = 8.7, 7.3 Hz, 1 H, H-4), 2.75 (dd, *J* = 7.5, 7.2 Hz, 2 H, CH_2S), 1.51-1.58 (m, 2 H, CH_2), 1.37-1.46 (m, 2 H, CH_2), 0.90 (dd, 7.4, 7.2 Hz, 3 H, CH_3); ^{13}C NMR δ 145.8, 142.5, 132.5, 127.0, 122.7, 115.6, 35.0, 31.6, 21.7, 13.6; MS (EI) *m/z* 226 (M^+,100%), 209 (15), 192 (25); HRMS (EI) calc. for $C_{10}H_{14}N_2O_2S$ (M^+) *m/z* 226.0776, found 226.0770; (ii) 4-(butylsulfanyl)-2-nitroaniline (**1o**) (1.12 g, 19%) as a red oil, ^{1}H NMR δ 8.16 (d, *J* = 2.2 Hz, 1 H, H-3), 7.39 (dd, *J* = 8.7, 2.2 Hz, 1 H, H-5), 6.76 (d, *J* = 8.7 Hz, 1 H, H-6), 6.06 (br s, 2 H, NH_2), 2.83 (dd, *J* = 7.3, 7.2 Hz, 2 H, CH_2S), 1.56-1.62 (m, 2 H, CH_2), 1.38-1.48 (m, 2 H, CH_2), 0.91 (dd, *J* = 7.4, 7.3 Hz, 3 H, CH_3); ^{13}C NMR δ 143.5, 139.1, 132.2, 128.3, 123.9, 119.3, 35.3, 31.2, 21.8, 13.6; MS (EI) *m/z* 226 (M^+, 100%), 170 (80); HRMS (EI) calc. for $C_{10}H_{14}N_2O_2S$ (M^+) *m/z* 226.0776, found 226.0772; and (iii) 2-(butylsulfanyl)-4-nitroaniline (**8**) (0.76 g, 13%) as a red oil, ^{1}H NMR δ 8.16 (d, *J* = 2.6 Hz, 1 H, H-3), 8.00 (dd, *J* = 9.1, 2.6 Hz, 1 H, H-5), 6.68 (d, *J* = 9.1 Hz, 1 H, H-6), 5.07 (br s, 2 H, NH_2), 2.79 (dd, *J* = 7.2, 6.6 Hz, 2 H, CH_2S), 1.52-1.60 (m, 2 H, CH_2), 1.38-1.47 (m, 2 H CH_2), 0.91 (t, *J* = 7.3 Hz, 3 H, CH_3); ^{13}C NMR δ 153.5, 138.7, 131.4, 125.7, 118.1, 113.0, 34.7, 31.5, 21.7, 13.6.

7-(Butylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide (3o). Method A using **1o** gave **3o** (68%) as a red solid, mp (MeOH/$CHCl_3$) 215-217 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.87 (d, *J* = 2.1 Hz, 1 H, H-8), 7.68 (dd, *J* = 8.9, 2.1 Hz, 1 H, H-6), 7.46 (d, *J* = 8.9 Hz,

1 H, H-5), 7.07 (br s, 2 H, NH_2), 3.04 (dd, J = 7.3, 7.2 Hz, 2 H, CH_2S), 1.55-1.63 (m, 2 H, CH_2), 1.37-1.45 (m, 2 H, CH_2), 0.88 (t, J = 7.3 Hz, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 160.0, 147.3, 135.9, 133.9, 130.0, 126.4, 115.8, 31.6, 30.1, 21.2, 13.4; Anal. calc. for $C_{11}H_{14}N_4OS$: C, 52.8; H, 5.6; N, 22.4; found C, 52.9; H, 5.8; N, 22.2%.

Example 18

7-Nitro-1,2,4-benzotriazin-3-amine 1-oxide (3p). Method B using 1-chloro-2,4-dinitrobenzene (**2p**) gave **3p** (15%) as a yellow powder, mp (DMF) 269-272 °C [lit.(Pazdera & Potacek, *Chem. Papers* **1988**, *42*, 527-537) mp (pyridine/EtOH) 290 °C]; ^1H NMR [$(CD_3)_2SO$] δ 8.82 (d, J = 2.6 Hz, 1 H, H-8), 8.44 (dd, J = 9.4, 2.6 Hz, 1 H, H-6), 8.03 (br s, 2 H, NH_2), 7.64 (d, J = 9.3 Hz, 1 H, H-5).

Example 19

6-Methoxy-1,2,4-benzotriazin-3-amine 1-oxide (3q).

5-Methoxy-2-nitroaniline (1q). A mixture of 5-methoxy-2-nitrobenzoic acid (**10**) (10 g, 50.7 mmol) diphenylphosphorylazide (DPPA) (11.5 mL, 53.3 mmol) and Et_3N (7.4 mL, 53.3 mmol) in t-BuOH (200 mL) was heated at reflux temperature for 16 h. The solution was cooled to 20 °C and the solvent evaporated. The residue was dissolved in DCM (300 mL) and washed with water (2 × 100 mL), saturated aqueous $KHCO_3$ (100 mL), brine (50 mL), dried, and the solvent evaporated. The residue was suspended in MeOH (250 mL), cHCl (50 mL) added, and the mixture stirred at 20 °C for 96 h. The solvent was evaporated and the residue suspended in saturated aqueous $KHCO_3$ (400 mL) and stirred for 30 min. The suspension was filtered, the solid washed with water (20 mL) and dried at 80 °C under reduced pressure. The solid was chromatographed, eluting with a gradient (20-30%) of EtOAc/pet. ether, to give **1q** (8.26 g, 98%); as a yellow solid, mp 128-130 °C [lit. (Seko et. al., *J. Chem. Soc. Perkin Trans. 1* **1999**, 1437) mp 130-132 °C]; ^1H NMR δ 8.07 (d, J = 9.5 Hz, 1 H, H-3), 6.28 (dd, J = 9.5, 2.6 Hz, 1 H, H-4), 6.21 (br s, 2 H, NH_2), 6.15 (d, J = 2.6 Hz, 1 H, H-6), 3.83 (s, 3 H, OCH_3); ^{13}C NMR δ 165.4, 147.1, 128.5, 126.9, 106.7, 99.4, 55.7.

6-Methoxy-1,2,4-benzotriazin-3-amine 1-oxide (3q). Method A using 5-methoxy-2-nitroaniline (**1q**) gave **3q** (63%) as a yellow powder, mp ($CHCl_3$) 265-270 °C; ^1H NMR [$(CD_3)_2SO$] δ 8.04 (d, J = 9.5 Hz, 1 H, H-8), 7.24 (br s, 2 H, NH_2), 6.95 (dd, J = 9.5, 2.6 Hz, 1 H, H-7), 6.86 (d, J = 2.6 Hz, 1 H, H-5), 3.91 (s, 3 H, OCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 164.7, 160.7, 151.3, 125.0, 121.5, 117.0, 103.8, 56.0; MS (EI^+) *m/z* 192

(M^+, 100%), 176 (5); HRMS (EI) calc. for $C_8H_8N_4O_2$ (M^+) *m/z* 192.0647, found 192.0653; Anal. calc. for $C_8H_8N_4O_2$: C, 50.0; H, 4.2; N, 29.2; found C, 50.0; H, 4.0; N, 29.0%.

Example 20

6-Methyl-1,2,4-benzotriazin-3-amine 1-oxide (3r). Method A using 5-methyl-2-nitroaniline (**1r**) gave **3r** (87%) as a yellow powder, mp (DMF) 263 °C (dec.) [lit. (Friebe et. al., *US Patent* 5,856,325, Jan 1999) mp (HOAc) 284-286 °C]; ^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (d, *J* = 8.8 Hz, 1 H, H-8), 7.33 (s, 1 H, H-5), 7.27 (br s, 2 H, NH_2), 7.18 (dd, *J* = 8.8, 1.7 Hz, 1 H, H-7), 2.42 (s, 3 H, CH_3); Anal. calc. for $C_8H_8N_4O$: C, 54.5; H, 4.6; N, 31.8; found C, 54.9; H, 4.6; N, 31.9%.

Example 21

6-Phenyl-1,2,4-benzotriazin-3-amine 1-oxide (3s). Method A using 4-nitro[1,1'-biphenyl]-3-amine (**1s**) gave **3s** (50%) as a yellow powder, mp (MeOH/DCM) 256-258 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.11 (d, *J* = 8.9 Hz, 1 H, H-8), 7.82 (br d, *J* = 7.2 Hz, 2 H, H-2', H-6'), 7.75 (d, *J* = 1.9 Hz, 1 H, H-5), 7.67 (dd, *J* = 8.9, 1.8 Hz, 1 H, H-7), 7.47-7.50 (m, 2 H H-3', H-5'), 7.47-7.50 (m, 1 H, H-4'), 7.38 (br s, 2 H, NH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 160.5, 149.1, 146.9, 138.0, 129.1 (2), 129.0, 128.9, 127.2 (2), 123.7, 122.5, 120.5; Anal. calc. for $C_{13}H_{10}N_4O$: C, 65.5; H, 4.2; N, 23.5; found C, 65.4; H, 4.2; N, 23.7%.

Example 22

6-Fluoro-1,2,4-benzotriazin-3-amine 1-oxide (3t). Method A using 5-fluoro-2-nitroaniline (**1t**) gave **3t** (61%) as a yellow powder, mp (DCM/pet. ether) 276-280 °C [lit. (Suzuki & Kawakami, *Synthesis* **1977**, 855) mp 268 °C]; ^{1}H NMR [$(CD_3)_2SO$] δ 8.21 (dd, *J* = 9.5, 5.9 Hz, 1 H, H-8), 7.50 (br s, 2 H, NH_2), 7.30 (dd, *J* = 10.0, 2.6 Hz, 1 H, H-5), 7.21 (ddd, *J* = 8.8, 7.5, 2.6 Hz, 1 H, H-7); ^{13}C NMR [$(CD_3)_2SO$] δ 164.5 (d, *J* = 254.6 Hz), 160.8, 150.6 (d, *J* = 16.1 Hz), 127.4, 123.4 (d, *J* = 11.1 Hz), 114.1 (d, *J* = 26.2 Hz), 109.5 (d, *J* = 23.1 Hz); Anal. calc. for $C_7H_5FN_4O$: C, 46.7; H, 2.8; N, 31.1; F, 10.6; found C, 46.5; H, 2.7; N, 31.3; F, 10.8%.

Example 23

6-Chloro-1,2,4-benzotrazin-3-amine 1-oxide (3u). Method A using 5-fluoro-2-nitroaniline (**1u**) gave **3u** (53%) as a yellow solid, mp (DCM/pet. ether) >320 °C [lit. (Friebe et. al., *US Patent* 5,856,325, Jan 1999) mp (HOAc) >300 °C]; ^{1}H NMR

$[(CD_3)_2SO]$ δ 8.13 (d, *J* = 9.2 Hz, 1 H, H-8), 7.60 (d, *J* = 2.11 Hz, 1 H, H-5), 7.53 (br s, 2 H, NH_2), 7.33 (dd, *J* = 9.2, 2.1 Hz, 1 H, H-7).

Example 24

6-Trifluoromethyl-1,2,4-benzotriazin-3-amine 1-oxide (3v). Method A using 5-trifluoromethyl-2-nitroaniline (**1v**) gave **3v** (29%) as a yellow solid, mp (DCM/pet. ether) 280-284 °C (dec.); ^{1}H NMR $[(CD_3)_2SO]$ δ 8.31 (d, *J* = 8.9 Hz, 1 H, H-8), 7.85 (br s, 1 H, H-5), 7.65 (br s, 2 H, NH_2), 7.56dd, *J* = 8.9, 1.6 Hz, 1 H, H-7); ^{13}C NMR $[(CD_3)_2SO]$ δ 160.8, 148.4, 134.8 (q, *J* = 32.7 Hz), 131.5, 123.5 (q, *J* = 4.0 Hz), 123.1 (q, *J* = 273.1 Hz), 122.0, 119.3; Anal. calc. for $C_8H_5F_3N_4O$: C, 41.8; H, 2.2; N, 24.3; F, 24.8; found C, 41.1; H, 2.1; N, 24.3; F, 24.6%.

Example 25

6-(Methylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide (3w). Method A using 5-methylsulfanyl-2-nitroaniline (**1w**) (Seko et. al., *J. Chem. Soc. Perkin Trans. 1* **1999**, 1437) gave **3w** (55%) as a yellow powder, mp (MeOH/$CHCl_3$) 248-250 °C; ^{1}H NMR $[(CD_3)_2SO]$ δ 7.99 (d, *J* = 8.3 Hz, 1 H, H-8), 7.30 (br s, 2 H, NH_2), 7.16-7.19 (m, 2 H, H-5, H-7), 2.59 (s, 3 H, SCH_3); ^{13}C NMR $[(CD_3)_2SO]$ δ 160.7, 149.2, 149.1, 127.3, 122.9, 119.8, 118.0, 14.0; Anal. calc. for $C_8H_8N_4OS$: C, 46.1; H, 3.9; N, 26.9; found C, 46.0; H, 3.8; N, 27.0%.

Example 26

6-(Butylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide (3x).

5-(Butylsulfanyl)-2-nitroaniline (1x). A solution of LiSnBu (3.34 g, 34.8 mmol) in DMF (30 mL) was added dropwise to a stirred solution of 5-chloro-2-nitroaniline (**1u**) (5.0 g, 30.0 mmol) in DMF (50 mL) at 20 °C and the mixture stirred for 2 h. The mixture was poured into water (300 mL) and extracted with EtOAc (2 × 150 mL). The combined organic fraction was washed with water (2 × 100 mL), brine (50 mL), dried, and the solvent evaporated. The residue was chromatographed, eluting with 20% EtOAc/pet. ether, to give **1x** (6.12 g, 90%) as a red solid, mp (EtOAc/pet. ether) 91-93 °C; ^{1}H NMR δ 8.00 (d, *J* = 7.5 Hz, 1 H, H-3), 6.52-6.56 (m, 2 H, H-4, H-6), 6.11 (br s, 2 H, NH_2), 2.96 (dd, *J* = 7.4, 7.3 Hz, 2 H, CH_2S), 1.66-1.73 (m, 2 H, CH_2), 1.44-1.53 (m, 2 H, CH_2), 0.96 (s, 3 H, CH_3); ^{13}C NMR δ 149.0, 144.8, 129.6, 126.4, 115.2, 113.4, 31.3, 30.6, 22.0, 13.6; Anal. calc. for $C_{10}H_{14}N_2O_2S$: C, 53.1; H, 6.2; N, 12.4; found C, 53.2; H, 6.3; N, 12.4%.

6-(Butylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide (3x). Method A using **1x** gave (i) starting material (**1x**) (60%) and (ii) **3x** (30%) as a red solid, mp (MeOH/$CHCl_3$) 180-182 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.99 (d, J = 9.1 Hz, 1 H, H-8), 7.31 (br s, 2 H, NH_2), 7.21 (d, J = 2.0 Hz, 1 H, H-5), 7.17 (dd, J = 9.1, 2.0 Hz, 1 H, H-7), 3.12 (dd, J = 7.3, 7.2 Hz, 2 H, CH_2S), 1.61-1.68 (m, 2 H, CH_2), 1.41-1.49 (m, 2 H, CH_2), 0.92 (s, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 160.6, 149.1, 147.9, 127.3, 123.4, 119.9, 118.8, 30.1, 29.9, 21.3, 13.4; Anal. calc. for $C_{11}H_{14}N_4OS$: C, 52.8; H, 5.6; N, 22.4; found C, 52.5; H, 5.6; N, 22.5%.

Example 27

5-Methoxy-1,2,4-benzotriazin-3-amine 1-oxide (3y). Method A using 6-methoxy-2-nitroaniline (**1y**) (Seko et. al., *J. Chem. Soc. Perkin Trans. 1* **1999**, 1437) gave **3y** (66%) as a yellow powder, mp (HOAc) 267 °C (dec.) [lit. (Friebe et. al., *US Patent* 5,856,325, Jan 1999) mp (HOAc) >270 °C]; ^{1}H NMR [$(CD_3)_2SO$] δ 7.65-7.69 (m, 1 H, H-7), 7.39 (br s, 2 H, NH_2), 7.23-7.27 (m, 2 H, H-6, H-8), 3.92 (s, 3 H, OCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 159.7, 153.3, 141.5, 130.0, 123.9, 113.4, 110.7, 55.9; Anal. calc. for $C_8H_8N_4O_2$: C, 50.0; H, 4.2; N, 29.2; found C, 50.2; H, 4.1; N, 29.1%.

Example 28

5-Methyl-1,2,4-benzotriazin-3-amine 1-oxide (3z). Method A using 6-methyl-2-nitroaniline (**1z**) gave **3z** (89%) as a yellow solid, mp (DCM/pet. ether) 253-255 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.98 (d, J = 8.6 Hz, 1 H, H-8), 7.64 (d, J = 7.1 Hz, 1 H, H-6), 7.33 (br s, 2 H, NH_2), 7.23 (dd, J = 8.6, 7.1 Hz, 1 H, H-7), 2.49 (s, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 156.7, 148.0, 135.1, 134.3, 129.8, 124.0, 117.4, 16.8; Anal. calc. for $C_8H_8N_4O$: C, 54.5; H, 4.6; N, 31.8; found C, 54.7; H, 4.7; N, 32.1%.

Example 29

5-Chloro-1,2,4-benzotriazin-3-amine 1-oxide (3aa). Method B using 1,2-dichloro-3-nitrobenzene (**2aa**) gave **3aa** (45%) as a yellow solid, mp (HOAc) 251-254 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.11 (dd, J = 8.7, 1.0 Hz, 1 H, H-8), 7.95 (dd, J = 7.6, 1.0 Hz, 1 H, H-6), 7.67 (br s, 2 H, NH_2), 7.29 (dd, J = 8.7, 7.6 Hz, 1 H, H-7); ^{13}C NMR [$(CD_3)_2SO$] δ 160.1, 145.7, 135.1, 131.1, 128.6, 123.6, 119.1; Anal. calc. for $C_7H_5ClN_4O$: C, 42.8; H, 2.6; N, 28.5; Cl, 18.0; found C, 43.0; H, 2.5; N, 28.3; Cl, 17.0%.

Exampl 30

5-Fluoro-1,2,4-benzotriazin-3-amine 1-oxide (3ab). Method A using 6-fluoro-2-nitroaniline (**1ab**) gave **3ab** (43%) as a yellow powder, mp (DMF) 252-256 °C [lit. (Suzuki & Kawakami, *Synthesis* **1977**, 855-857) mp 278 °C] ^{1}H NMR [$(CD_3)_2SO$] δ 7.96 (dd, *J* = 8.7, 1.0 Hz, 1 H, H-8), 7.66 (ddd, *J* = 10.3, 7.9, 1.2 Hz, 1 H, H-6), 7.61 (br s, 2 H, NH_2), 7.28 (ddd, *J* = 8.6, 8.0, 5.1 Hz, 1 H, H-7); ^{13}C NMR [$(CD_3)_2SO$] δ 160.1 (d, *J* = 5.6 Hz), 154.9 (d, *J* = 253.1 Hz), 139.7 (d, *J* = 16.1 Hz), 131.1 (d, *J* = 4.2 Hz), 122.8 (d, *J* = 7.6 Hz), 119.4 (d, *J* = 17.7 Hz), 115.8 (d, *J* = 4.4 Hz); Anal. calc. for $C_7H_5FN_4O$: C, 46.7; H, 2.8; N, 31.1; F, 10.6; found C, 46.6; H, 2.7; N, 31.2; F, 10.3%.

Example 31

5-Nitro-1,2,4-benzotriazin-3-amine-1-oxide (3ac). Method B using 2,6-dinitrofluorobenene (**2ac**) gave 1-oxide **3ac** (27%) as a yellow powder, mp (DCM/pet. ether) 269-272 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.38 (dd, *J* = 8.5, 1.1 Hz, 1 H, H-6), 8.32 (dd, *J* = 7.7, 1.2 Hz, 1 H, H-8), 7.88 (br s, 2 H, NH_2), 7.39 (dd, *J* = 8.5, 7.7 Hz, 1 H, H-7); ^{13}C NMR [$(CD_3)_2SO$] δ 160.5, 144 2, 141.5, 130.9, 129.7, 124.2, 122.0; HRMS (EI) calc. for $C_7H_5N_5O_3$ (M^+) *m/z* 207.0392, found 207.0393.

Example 32

5-Methylsulfanyl-1,2,4-benzotriazin-3-amine 1-oxide (3ad). Method A using 6-methylsulfanyl-2-nitroaniline (**1ad**) gave **3ad** (7%) as a yellow solid, mp (MeOH/DCM) 248-252 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.85 (dd, *J* = 8.7, 1.4 Hz, 1 H, H-8), 7.45-7.48 (m, 3 H, H-6, NH_2), 7.28 (dd, *J* = 8.7, 7.7 Hz, 1 H, H-7), 2.49 (s, 3 H, SCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 159.4, 145.9, 136.8, 129.4, 127.6, 124.3, 114.6, 13.5; Anal. calc. for $C_8H_8N_4OS$: C, 46.1; H, 3.9; N, 26.9; found C, 46.4; H, 3.8; N, 26.8%.

Example 33

***N*^{7},*N*^{7}-Dimethyl-1,2,4-benzotriazine-3,7-diamine 1-oxide (11).** A solution of 7-fluoro-1,2,4-benzotriazine-3-amine 1-oxide (**3k**) (114 mg, 0.63 mmol) and 40% aqueous dimethylamine (5 mL) in CH_3CN (15 mL) was stirred at 90 °C for 4 days. The solvent was evaporated and the residue was partitioned between dilute aqueous NH_3 (10 mL) and DCM (10 mL). The aqueous fraction was extracted with DCM (3 × 15 mL), the combined organic fraction dried, and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-2%) of MeOH/DCM, to give **11** (30 mg, 61%) as an orange powder, mp (DCM/hexane) 231-233 °C; ^{1}H NMR [$(CD_3)_2SO$]

δ 7.58 (dd, J = 9.4, 2.9 Hz, 1 H, H-6), 7.45 (d, J = 9.4 Hz, 1 H, H-5), 7.02 (d, J = 2.9 Hz, 1 H, H-8), 6.97 (br s, 2 H, NH_2), 3.05 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR [$(CD_3)_2SO$] δ 158.3, 147.6, 130.3, 126.5, 125.6, 95.3, 40.0; Anal. calc. for $C_9H_{11}N_5O$: C, 52.7; H, 5.4; N, 34.2; found, C, 52.4; H, 5.3; N, 34.2%.

Example 34

***N*^{6},*N*^{6}-Dimethyl-1,2,4-benzotriazine-3,6-diamine 1-oxide (12).** A solution of 6-fluoro-1,2,4-benzotriazine-3-amine 1-oxide (**3t**) (0.1 g, 0.55 mmol) and 40% aqueous solution of dimethylamine (5 mL) in CH_3CN (15 mL) was stirred at 20 °C for 5 days. The solvent was evaporated and the residue was partitioned between dilute aqueous NH_3 (10 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (3 × 15 mL), the combined organic extract dried, and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-3%) of MeOH/DCM, to give **12** (93 mg, 82%) as an orange powder, mp (DCM/hexane) 264-267 °C; ^1H NMR [$(CD_3)_2SO$] δ 7.92 (d, J = 9.7 Hz, 1 H, H-8), 6.97 (dd, J = 9.7, 2.7 Hz, 1 H, H-7), 6.88 (s, 2 H, NH_2), 6.33 (d, J = 2.7 Hz, 1 H, H-5), 3.09 [s, 6 H, $N(CH_3)_2$]; Anal. calc. for $C_9H_{11}N_5O$: C, 52.7; H, 5.4; N, 34.1; found C, 52.5; H, 5.40; N, 34.2%.

Example 35

***N*^{6},*N*^{6}-Diethyl-1,2,4-benzotriazine-3,6-diamine 1-oxide (13).** 6-Fluoro-1,2,4-benzotriazine-3-amine 1-oxide (**3t**) (0.1 g, 0.55 mmol) and diethylamine (3 mL) in CH_3CN (15 mL) was heated at 90 °C for 2 days.The solvent was evaporated and the residue was stirred in dilute ammonia (10 mL) and the resulting precipitate was filtered and chromatographed eluting with a gradient of 0-2% MeOH/DCM, to give **13** (83 mg, 65%) as an orange powder, mp (DCM/Hexane) 247-251 °C; ^1H NMR [$(CD_3)_2SO$] δ 7.91 (d, J = 9.8 Hz, 1 H, H-8), 6.93 (dd, J = 9.7, 2.8 Hz, 1 H, H-7), 6.83 (s, 2 H, NH_2), 6.31 (d, J = 2.6 Hz, 1 H, H-5), 3.47 (q, J = 7.0 Hz, 4 H, 2 × CH_2) 1.14 (t, J = 7.0 Hz, 6 H, 2 × CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 160.6, 152.1, 150.9, 121.8, 121.2, 113.9, 99.0, 44.2, 12.3; Anal. calc. for $C_{11}H_{15}N_5O$: C, 56.6; H, 6.5; N, 30.0; found C, 56.6; H, 6.6; N, 30.1%.

Example 36

7-(2-Methoxyethoxy)-1,2,4-benzotriazin-3-amine 1-oxide (14). A mixture of 7-hydroxy-1-oxide **3h** (1.00 g, 5.8 mmol), dry K_2CO_3 (2.40 g, 17.4 mmol) and 2-bromoethylmethylether (2.42 g, 17.4 mmol) in DMF (20 mL) was heated at 80 °C for 2 h. The solvent was evaporated and the residue chromatographed, eluting with a

gradient (0-3%) MeOH/DCM, to give compound **14** (1.06 g, 77 %) as a yellow powder, mp (DCM/pet. ether) 201 -203°C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.07 (d, *J* = 9.5 Hz, 1 H, H-5), 7.82 (br s, 2 H, NH_2), 7.76 (dd, *J* = 9.5, 2.6 Hz, 1 H, H-6), 7.50 (d, *J* = 2.6 Hz, 1 H, H-8), 4.26, (t, *J* = 4.3 Hz, 2 H, CH_2), 3.72 (t, *J* = 4.3 Hz, 2 H, CH_2), 3.33 (s, 3 H, OCH_3); Anal. calc. for $C_{10}H_{12}N_4O_5$: C, 50.8; H, 5.1; N, 23.7; found C, 51.1; H, 5.0; N, 23.7%.

Example 37

7-(2-Bromoethoxy)-1,2,4-benzotriazin-3-amine 1-oxide (15). A mixture of 7-hydroxy-1-oxide **3h** (1.23 g, 7.15 mmol), K_2CO_3 (1.97 g, 14.3 mmol) and 1,2-dibromoethane (4.0 ml) in DMF (20 ml) was heated at 80 °C for 20 h. The solvent was evaporated, and the residue stirred in water (100 mL). The resulting precipitate was filtered, washed with water (3 × 50 mL) and dried to give a yellow solid, which was chromatographed, eluting with 0-3% MeOH/DCM, to give 1-oxide **15** (1.0 g, 49%) as a yellow powder, mp (DCM/pet. ether) 228-230 °C; ^{1}H NMR δ 7.52-7.50 (m, 3 H, H-5, H-6, H-8), 7.12 (br s, 2 H, NH_2), 4.45 (t, *J* = 5.2 Hz, 2 H, CH_2), 3.85 (t, *J* = 5.2 Hz, 2 H, CH_2); HRMS (EI) calc. for $C_9H_9{}^{79}BrN_4O_2$ (M^+) *m/z* 283.9909, found 283.9902; calc. for $C_9H_9{}^{81}BrN_4O_2$ (M^+) *m/z* 285.9888, found 285.9881.

Example 38

***N*-{2-[(3-Amino-1-oxido-1,2,4-benzotriazin-7-yl)oxy]ethyl}-2,2,2-trifluoroacetamide (16).** A mixture of 7-hydroxy-1-oxide **3h** (520 mg, 3.02 mmol), K_2CO_3 (883 mg, 6.04 mmol) and *N*-(2-bromoethyl)-2,2,2-trifluoroacetamide (1.25 g, 6.03 mmol) in DMF (20 ml) was heated at 80 °C for 3 h. The solvent was evaporated and residue stirred in water (100 mL) the resulted precipitate was filtered, washed with water (3 × 50 mL), and dried to give a yellow solid, which was chromatographed, eluting with a gradient (0-3%) of MeOH/DCM, to give 1-oxide **16** (639 mg, 66%) as a yellow powder, mp (DCM/pet. ether) 234-246 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.66 (br s, 1 H, CONH), 7.52 (d, *J* = 9.2 Hz, 1 H, H-5), 7.51 (d, *J* = 2.3 Hz, 1 H, H-8), 7.42 (dd, *J* = 9.1, 2.9 Hz, 1 H, H-6) 7.12 (br s, 2 H, NH_2), 4.23 (t, *J* = 5.5 Hz, 2 H, CH_2), 3.63 (t, *J* = 5.4 Hz, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 159.5, 156.7 (q, *J* = 36.3 Hz), 155.1, 144.9, 129.7, 128.4, 127.4, 119.8, 115.8 (q, *J* = 287.8 Hz), 99.0, 65.9; Anal. calc. for $C_{11}H_{10}F_3N_5O_3$: C, 41.7; H, 3.2; N, 22.2; F, 18.0; found C, 42.0; H, 3.0; N, 21.9; F, 17.5%.

Exampl 39

7-[2-(4-Morpholinyl)ethoxy]-1,2,4-benzotriazin-3-amin 1-oxide (17). A mixture of 7-hydroxy-1-oxide **3h** (1.15 g, 6.7 mmol), K_2CO_3 (3.77 g, 20.0 mmol) and 4-(2-chloroethyl)morpholine hydrochloride (2.49 g, 13.4 mmol) in DMF (25 ml) was heated at 80 °C for 2 h. The solvent was evaporated, the residue stirred in water (100 mL), the resulting precipitate filtered, washed with water (3 × 50 mL), and dried to give 1-oxide **17** (1.53 g, 79%) as a yellow solid, mp (DCM/pet. ether) 175-181 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.52-7.46 (m, 3 H, H-5, H-6, H-8), 7.09 (br s, 2 H, NH_2), 4.20 (t, J = 5.6 Hz, 2 H, CH_2), 3.58 (t, J = 4.7 Hz, 4 H, 2 × CH_2), 2.73 (t, J = 5.6 Hz, 2 H, CH_2), 2.49 (t, J = 4.6 Hz, 4 H, 2 × CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 159.5, 155.5, 144.8, 129.7, 128.5, 127.3, 98.8, 66.1 (2), 56.7, 53.5 (2); Anal. calc. for $C_{13}H_{17}N_5O_3$: C, 53.6; H, 5.9; N, 24.0; found C, 53.5; H, 6.0; N, 23.8%.

Example 40

1,2,4-Benzotriazin-3-amine 1-oxide (3). A mixture of 2-nitroaniline (**1**) (10.0 g, 72.4 mmol) and cyanamide (15.2 g, 0.36 mmol) was melted at 100 °C, cooled to ca. 40 °C, cHCl (20 mL) added carefully. The exotherm was allowed to subside and the mixture was heated at 100 °C for 1 h. The mixture was cooled to ca. 40 °C and 30% NaOH solution (30 mL) added carefully. The mixture was stirred at 100 °C for 2 h, cooled to 25 °C, diluted with water (50 mL) and stirred for 30 min. The suspension was filtered, washed with water (2 × 10 mL), ether (2 × 5 mL) and dried under vacuum to give 1-oxide **3** (10.3 g, 88%) as a yellow powder, mp (MeOH/EtOAc) 267-269 °C [lit. (Arndt, *Ber.* **1913**, *46*, 3522) mp (EtOH) 269 °C]; ^{1}H NMR δ 8.13 (d, J = 8.7 Hz, 1 H, H-8), 7.79 (dd, J = 8.6, 7.0 Hz, 1 H, H-6), 7.54 (d, J = 8.6 Hz, 1 H, H-5), 7.32-7.38 (m, 3 H, H-7, NH_2).

Example 41

3-Chloro-1,2,4-benzotriazine 1-oxide (19). A solution of $NaNO_2$ (10 g, 0.145 mol) in water (100 mL) added dropwise to a suspension of 1-oxide **3** (11.7 g, 72.2 mmol) in 2 M HCl (300 mL) at 5 °C and the mixture stirred vigorously until the foaming subsided (2 h). The resulting precipitate was filtered, dissolved in dilute aqueous NH_3, filtered, and acidified with cHCl. The precipitate was filtered, washed with water and dried to give 3-hydroxy-1,2,4-benzotriazine 1-oxide (**18**) (5.77 g, 49%) as a yellow powder, mp 209-212 °C; [lit. (Robbins *et al.*, *J. Chem. Soc.* **1957**, 3186) mp (H_2O) 219 °C]; ^{1}H NMR δ 8.14 (d, J = 8.4 Hz, 1 H, H-8), 7.77-7.81 (m, 1 H, H-6), 7.54 (d, J = 8.4 Hz, 1

H, H-5), 7.90 (m, 3 H, H-7, NH_2); ^{13}C NMR δ 160.2, 148.7, 135.6, 129.8, 125.8, 124.6, 119.8.

A mixture of alcohol **18** (5.7 g, 34.9 mmol), *N,N*-dimethylaniline (11 mL, 87.3 mmol), and $POCl_3$ (23 mL, 244 mmol) was heated at reflux temperature for 1 h then poured on to ice. The resulting solid was filtered and recrystallized to give chloride **19** (3.77 g, 59%) as a pale yellow powder, mp (MeOH) 119-119.5 °C [lit. (Robbins *et al.*, *J. Chem. Soc.*, **1957**, 3186) mp (MeOH) 117-118 °C]; ^1H NMR δ 8.38 (dd, *J* = 8.7, 1.0 Hz, 1 H, H-8), 8.16 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H, H-6), 8.06 (dd, *J* = 8.2, 1.0 Hz, 1 H, H-5), 7.90 (ddd, *J* = 8.7, 6.9, 1.3 Hz, 1 H, H-7); ^{13}C NMR δ 155.3, 146.9, 137.2, 133.9, 131.5, 128.0, 119.9.

Example 42

Ethyl [(1-oxido-1,2,4-benzotriazin-3-yl)amino]acetate (20). A mixture of chloride **19** (2.02 g, 11.1 mmol), glycine ethyl ester hydrochloride (2.33 g, 16.7 mmol) and Et_3N (4.2 mL, 30 mmol) in DME (100 mL) was heated at reflux temperature for 6 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and water (100 mL), the aqueous fraction extracted with DCM (2 × 50 mL), the combined organic fraction dried , and the solvent evaporated. The residue was chromatographed, eluting with 10%EtOAc/DCM, to give ester **20** (2.75 g, 99%) as a yellow solid, mp (EtOAc/DCM) 136-138 °C; ^1H NMR δ 8.27 (dd, *J* = 8.6, 1.0 Hz, 1 H, H-8), 7.72 (ddd, *J* = 8.5, 7.0, 1.4 Hz, 1 H, H-6), 7.62 (dd, *J* = 8.5, 1.0 Hz, 1 H, H-5), 7.34 (ddd, *J* = 8.6, 7.0, 1.0 Hz, 1 H, H-7), 5.87 (br s, 1 H, NH), 4.30 (d, *J* = 5.7 Hz, 2 H, CH_2N), 4.26 (q, *J* = 7.2 Hz, 2 H, CH_2O), 1.31 (t, *J* = 7.2 Hz, 3 H, CH_3); ^{13}C NMR δ 169.9 (CO_2), 158.4 (C-3), 148.5 (C-4a), 135.6 (C-6), 131.2 (C-8a), 126.7 (C-5), 125.5 (C-7), 120.4 (C-8), 61.6 (CH_2O), 43.2 (CH_2N), 14.2 (CH_3); Anal. calc. for $C_{11}H_{12}N_4O_3$: C, 53.2; H, 4.9; N, 22.6; found C, 53.4; H, 5.0; N, 22.6%.

Example 43

[(1-Oxido-1,2,4-benzotriazin-3-yl)amino]acetic acid (21). A solution of ester **20** (0.75 g, 3.0 mmol) and 1 M NaOH (15 mL, 15.0 mmol) in MeOH (50 mL) was stirred at 20 °C for 2 h. The solution was washed with ether (2 × 50 mL), the volume reduced to 20 mL, and the pH adjusted to 3 with 5 M HCl. The precipitate was filtered and recrystallized to give acid **21** (576 mg, 86%) as a pale yellow solid, mp (water) 217-219 °C; ^1H NMR [$(CD_3)_2SO$] δ 8.14 (d, *J* = 8.6 Hz, 1 H, H-8), 8.08 (br. s, 1 H, NH), 7.80 (ddd, *J* = 8.6, 7.1, 1.1 Hz, 1 H, H-6), 7.59 (d, *J* = 8.6 Hz, 1 H, H-5), 7.37 (ddd, *J* = 8.6, 7.1, 1.1 Hz, 1 H, H-7), 4.01 (br s, 2 H, CH_2N), CO_2H not observed; ^{13}C

NMR [$(CD_3)_2SO$] δ 171.3 (CO_2), 158.8 (C-3), 148.0 (C-4a), 135.8 (C-6), 130.2 (C-8a), 126.1 (C-5), 125.0 (C-7), 119.8 (C-8), 42.6 (CH_2N); Anal. calc. for $C_9H_8N_4O_3.¼H_2O$: C, 48.1; H, 3.8; N, 24.9; found C, 48.2; H, 3.8; N, 24.2%.

Example 44

2-[(1-Oxido-1,2,4-benzotriazin-3-yl)amino]ethanol (22). A solution of chloride **19** (536 mg, 3.0 mmol) and ethanolamine (0.53 mL, 8.9 mmol) was heated at reflux temperature in DME (50 mL) for 1 h. The mixture was cooled to 20 °C, the solvent evaporated, and the residue partitioned between dilute aqueous NH_3 (50 mL) and DCM (100 mL). The organic fraction was dried , and the solvent evaporated. The residue was chromatographed, eluting with 5% MeOH/DCM, to give alcohol **22** (533 mg, 88%) as a yellow solid, mp (MeOH/DCM) 214-218 °C; ^1H NMR [$(CD_3)_2SO$] δ 8.13 (dd, *J* = 8.5, 1.0 Hz, 1 H, H-8'), 7.82 (br s, 1 H, NH), 7.78 (ddd, *J* = 8.4, 7.0, 1.0 Hz, 1 H, H-6'), 7.57 (d, *J* = 8.4, Hz, 1 H, H-5'), 7.34 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1 H, H-7'), 4.74 (t, *J* = 5.6 Hz, 1 H, OH), 3.56-3.61 (m, 2 H, CH_2), 3.40-3.45 (m, 2 H, CH_2N); ^{13}C NMR [$(CD_3)_2SO$] δ 159.0 (C-3'), 148.2 (C-4a'), 135.7 (C-6'), 130.0 (C-8a'), 125.9 (C-5'), 124.4 (C-7'), 119.8 (C-8'), 59.2 (CH_2O), 43.2 (CH_2N); Anal. calc. for $C_9H_{10}N_4O_2$: C, 52.4; H, 4.9; N, 27.2; found C, 52.3; H, 4.8; N, 26.6%.

Example 45

***N*-(2-Methoxyethyl)-1,2,4-benzotriazin-3-amine 1-oxide (23)**. A solution of chloride **19** (783 mg, 4.3 mmol) and 2-methoxyethylamine (0.82 mL, 9.5 mmol) in DME (70 mL) was heated at reflux temperature for 5 h. The cooled solution was partitioned betwen EtOAc (100 mL) and water (100 mL). The aqueous fraction was extracted with EtOAc (50 mL), the combined organic fractioned dried, and the solvent evaporated. The residue was chromatographed, eluting with a gradient (10-30%) EtOAc/DCM, to give 1-oxide **23** (915 mg, 96%) as a yellow powder, mp (EtOAc/DCM) 154-156 °C; ^1H NMR δ 8.26 (dd, *J* = 8.6, 1.3 Hz, 1 H, H-8), 7.71 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1 H, H-6), 7.60 (br d, *J* = 8.4 Hz, 1 H, H-5), 7.30 (ddd, *J* = 8.6, 7.1, 1.4 Hz, 1 H, H-7), 5.71 (br s, 1 H, NH), 3.72 (dt, *J* = 5.5, 5.3 Hz, 2 H, CH_2N), 3.61 (dd, *J* = 5.3, 5.0 Hz, 2 H, CH_2O), 3.40 (s, 3 H, CH_3O); ^{13}C NMR δ 158.8 (C-3), 148.5 (C-4a), 135.6 (C-6), 131.0 (C-8a), 126.3 (C-5), 125.74 (C-7), 120.5 (C-8), 70.8 (CH_2O), 58.9 (OCH_3), 41.1 (CH_2N); Anal. calc. for $C_{10}H_{12}N_4O_2$: C, 54.5; H, 5.5; N, 25.4; found C, 54.8; H, 5.3; N, 25.3%.

Example 46

3-[(1-Oxido-1,2,4-benzotriazin-3-yl)amino]propanol (24). A solution of chloride **19** (710 mg, 3.9 mmol) and 3-amino-1-propanol (0.75 mL, 9.8 mmol) was heated at reflux temperature in DME (50 mL) for 1 h. The mixture was cooled to 20 °C, the solvent evaporated, and the residue partitioned between dilute aqueous NH_3 (50 mL) and DCM (100 mL). The organic fraction was dried , and the solvent evaporated. The residue was chromatographed, eluting with 5% EtOAc/DCM, to give alcohol **24** (828 mg, 96%) as a yellow solid, mp (MeOH/DCM) 155-156 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.13 (dd, *J* = 8.6, 1.1 Hz, 1 H, H-8'), 7.87 (br s, 1 H, NH), 7.78 (ddd, *J* = 8.4, 7.1, 1.1 Hz, 1 H, H-6'), 7.57 (d, *J* = 8.4, Hz, 1 H, H-5'), 7.34 (ddd, *J* = 8.6, 7.1, 1.1 Hz, 1 H, H-7'), 4.51 (t, *J* = 5.1 Hz, 1 H, OH), 3.50-3.55 (m, 2 H, CH_2), 3.40-3.45 (m, 2 H, CH_2N), 1.72-1.79 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 158.9 (C-3'), 148.3 (C-4a'), 135.6 (C-6'), 129.9 (C-8a'), 125.9 (C-5'), 124.3 (C-7'), 119.8 (C-8'), 58.4 (CH_2O), 37.9 (CH_2N), 31.7 (CH_2); Anal. calc. for $C_{10}H_{12}N_4O_2$; C, 54.5; H, 5.5; N, 25.5; found C, 54.9; H, 5.6; N, 25.6%.

Example 47

2-[(1-Oxido-1,2,4-benzotriazin-3-yl)amino]acetonitrile (25). A solution of chloride **19** (790 mg, 4.4 mmol), 2-aminoacetonitrile hydrochloride (0.81 g, 8.7 mmol) and Et_3N (1.2 mL, 8.7 mmol) in DME (80 mL) was stirred at reflux temperature for 6 h. The solution was partitioned between DCM (100 mL) and water (100 mL), the aqueous fraction washed with DCM (2 × 50 mL), the combined organic fraction dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (5-20%) of EtOAc/DCM, to give nitrile **25** (383 mg, 44%) as yellow needles, mp (EtOAc/DCM) 233-237 °C; ^{1}H NMR δ 8.33 (dd, *J* = 8.5, 1.2 Hz, 1 H, H-8'), 7.83 (ddd, *J* = 8.4, 7.1, 1.2 Hz, 1 H, H-6'), 7.76 (d, *J* = 8.4 Hz, 1 H, H-5'), 7.45 (ddd, *J* = 8.5, 7.1, 1.2 Hz, 1 H, H-7'), 5.68 (br s, 1 H, NH), 4.49 (d, *J* = 6.3 Hz, 2 H, CH_2); Anal. calc for $C_9H_7N_5O$: C, 53.7; H, 3.5; N, 34.8; found C, 54.0; H, 3.2; N, 34.9%.

Example 48

3-[(1-Oxido-1,2,4-benzotriazin-3-yl)amino]propanenitrile (26). A solution of chloride **19** (776 mg, 4.3 mmol), 3-aminopropanenitrile fumarate (2.74 g, 21.4 mmol) and Et_3N (3.6 mmol, 25.6 mmol) in DME (50 mL) was stirred at reflux temperature for 6 h. The solution was partitioned between DCM (100 mL) and water (100 mL), the aqueous fraction washed with DCM (2 × 50 mL), the combined organic fraction dried and the solvent evaporated. The residue was chromatographed, eluting with 10%

EtOAc/DCM, to give nitrile **26** (771 mg, 84%) as yellow needles, mp (EtOAc/DCM) 191-193 °C; ^{1}H NMR δ 8.29 (dd, *J* = 8.7, 1.1 Hz, 1 H, H-8'), 7.76 (ddd, *J* = 8.5, 7.0, 1.1 Hz, 1 H, H-6'), 7.64 (dd, *J* = 8.5, 1.0 Hz, 1 H, H-5') 7.37 (ddd, *J* = 8.7, 7.0, 1.0 Hz, 1 H, H-7'), 6.00 (br s, 1 H, NH), 3.87 (q, *J* = 6.5 Hz, 2 H, H-3), 2.85 (t, *J* = 6.5 Hz, 2 H, H-2); ^{13}C NMR δ 158 (C-3'), 148.4 (C-4a'), 135.9 (C-6'), 131.3 (C-8a'), 126.7 (C-5'), 120.4 (C-8'), 117.9 (C-1), 37.6 (C-3), 18.1 (C-2); Anal. calc. for $C_{10}H_9N_5O$: C, 55.8; H, 4.2; N, 32.6; found, C, 55.9; H, 4.3; N, 32.6%.

Example 49

4-[(1-Oxido-1,2,4-benzotriazin-3-yl)amino]butanenitrile (27). A solution of chloride **19** (1.82 g, 10.0 mmol) and 4-aminobutanenitrile (2.11 g, 25.0 mmol) in DME (100 mL) was heated at reflux temperature for 4 h. The cooled solution was partitioned betwen EtOAc (200 mL) and water (200 mL). The aqueous fraction was extracted with EtOAc (100 mL), the combined organic fractioned dried, and the solvent evaporated. The residue was chromatographed, eluting with a gradient (5-10%) EtOAc/DCM, to give 1-oxide **27** (1.80 g, 79%) as a yellow powder, mp (EtOAc/DCM) 184-187 °C; ^{1}H NMR δ 8.26 (dd, *J* = 8.7, 1.3 Hz, 1 H, H-8'), 7.73 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1 H, H-6'), 7.63 (d, *J* = 8.4 Hz, 1 H, H-5'), 7.33 (ddd, *J* = 8.7, 7.0, 1.3 Hz, 1 H, H-7'), 6.00 (br s, 1 H, NH), 3.72 (dd, *J* = 6.6, 6.4 Hz, 2 H, H-4), 2.51 (t, J = 7.2 Hz, 2 H, H-2), 2.07-2.14 (m, 2 H, H-3); ^{13}C NMR δ 158.7 (C-3'), 148.2 (C-4a'),135.8 (C-6'), 131.0 (C-8a'), 126.4 (C-5'), 125.4 (C-7'), 120.4 (C-8'), 119.2 (C-1), 40.0 (C-4), 25.4 (C-2), 14.8 (C-3); Anal. calc. for $C_{11}H_{11}N_5O$: C, 57.6; H, 4.8; N, 30.6; found C, 57.8; H, 5.1; N, 30.8%.

Example 50

***N*-(3-Azidopropyl)-1,2,4-benzotriazin-3-amine 1-oxide (28).** A solution of chloride **19** (2.18 g, 12.0 mmol) and 3-azido-1-propanamine hydrochloride (2.46 g, 18.0 mmol) and Et_3N (5.0 mL, 36.0 mmol) in DCM (100 mL) was heated at reflux temperature for 16 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (5-10%) of EtOAc/DCM, to give 1-oxide **28** (2.49 g, 85%) as a yellow powder, mp (EtOAc/DCM) 128-130 °C; ^{1}H NMR δ 8.26 (dd, *J* = 8.7, 1.4 Hz, 1 H, H-8'), 7.71 (ddd, *J* = 8.3, 7.1, 1.4 Hz, 1 H, H-6'), 7.61 (d, *J* = 8.3 Hz, 1 H, H-5'), 7.30 (ddd, *J* = 8.7, 7.1, 1.1 Hz, 1 H, H-7'), 5.73 (br s, 1 H, NH), 3.67 (dd, *J* = 6.6, 6.4 Hz, 2 H, CH_2N), 3.47 (t, *J* = 6.5 Hz, 2 H, CH_2N_3), 1.95-2.03 (m, 2 H, CH_2); ^{13}C NMR δ 158.9 (C-3'), 148.8 (C-4a'), 135.6 (C-6'), 130.9 (C-8a'), 126.6 (C-5'), 125.0 (C-7'),

120.4 (C-8'), 49.2 (CH_2N_3), 38.8 (CH_2N), 28.6 (CH_2); Anal. calc. for $C_{10}H_{11}N_7O$: C, 50.0; H, 4.5; N, 40.0; found C, 49.1; H, 4.6; N, 40.3%.

Example 51

***tert*-Butyl 3-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]propylcarbamate (29).** A solution of chloride **19** (4.0 g, 22.0 mmol), *tert*-butyl 3-aminopropylcarbamate (5.76 g, 33.0 mmol) and Et_3N (4.6 mL, 33.0 mmol) in DCM (150 mL) was stirred at 20 °C for 5 days. The solvent was evaporated and the residue chromatographed, eluting with 20% EtOAc/DCM, to give 1-oxide **29** (5.21 g, 74%) as a yellow powder, mp (EtOAc/DCM) 145-147 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.13 (dd, J = 8.6, 1.1 Hz, 1 H, H-8'), 7.84 (s, 1 H, NH), 7.78 (ddd, J = 8.4, 7.1, 1.1 Hz, 1 H, H-6'), 7.56 (d, J = 8.4 Hz, 1 H, H-5'), 7.32 (ddd, J = 8.6, 7.1, 1.1 Hz, 1 H, H-7'), 6.83 (t, J = 5.3 Hz, 1 H, $NHCO_2$), 3.32-3.36 (m, 2 H, H-1), 2.99-3.04 (m, 2 H, H-3), 1.66-1.73 (m, 2 H, H-2), 1.37 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 158.9, 155.6, 148.2, 135.7, 130.0, 125.9, 124.4, 119.9, 77.4, 38.2, 37.5, 28.9, 28.2 (3); Anal. calc. for $C_{15}H_{21}N_5O_3$: C, 56.4; H, 6.6; N, 21.9; found: C, 56.4; H, 6.6; N, 22.1%.

Example 52

***tert*-Butyl 3-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]propyl(ethyl)carbamate (32).**

***tert*-Butyl 2-cyanoethyl(ethyl)carbamate (30)**. A solution of ethylamine (6.1 mL, 76 mmol) was added dropwise to stirred acrylonitrile (10 mL) at 5 °C and the mixture allowed to warm to 20 °C over 1 h. The excess acrylonitrile was evaporated and the residue dissolved in DCM (100 mL). A solution of di-*tert*-butyldicarbonate (18.3 g, 84 mmol) in DCM (50 mL) added dropwise at 5 °C and then stirred at 20 °C for 16 h. The solution was diluted with DCM (100 mL), washed with dilute Na_2CO_3 solution (100 mL), 0.1 M HCl (100 mL), water (2 × 100 mL), and brine (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with 20% EtOAc/pet. ether, to give nitrile **30** (15.0 g, 99%) as an oil, ^{1}H NMR δ 3.47 (t, J = 6.7 Hz, 2 H, CH_2N), 3.20 (q, J = 7.1 Hz, 2 H, CH_2), 2.61 (br s, 2 H, CH_2), 1.48 [s, 9 H, $C(CH_3)_3$], 1.14 (t, J = 7.1 Hz, 3 H, CH_3); MS (EI) *m/z* 198 (M^+, 1%), 158 (2), 143 (5), 125 (20), 57 (100); HRMS (EI) calc. for $C_{10}H_{18}N_2O_2$ (M^+) *m/z* 198.1368, found 198.1367.

***tert*-Butyl 3-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]propyl(ethyl)carbamate (32).** A mixture of nitrile **30** (4.60 g, 23.2 mmol) and freshly prepared Raney Nickel (3 mL) in EtOH saturated with NH_3 was stirred under H_2 (60 psi) for 16 h. The mixture was

filtered through celite, washed with EtOH (4 × 10 mL), and the solvent evaporated to give *tert*-butyl 3-aminopropyl(ethyl)carbamate (**31**) (4.65 g, 99%) as an oil which was used without further characterization. Amine **31** (2.5 g, 12.3 mmol) was added to a stirred solution of chloride **19** (0.89 g, 4.9 mmol) in DME (50 mL) and the solution heated at 100 °C for 6 h. The solvent was evaporated and the residue partitioned between DCM (150 mL) and water (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (20-50%) of EtOAc/pet. ether, to give 1-oxide **32** (1.43 g, 84%) as a yellow solid, mp (EtOAc/pet ether) 64-66 °C; ^{1}H NMR δ 8.24 (d, *J* = 8.6 Hz, 1 H, H-8), 7.65-7.70 (m, 1 H, H-6), 7.57 (d, *J* = 8.4 Hz, 1 H, H-5), 7.24-7.28 (m, 1 H, H-7), 6.32 (br s, 1 H, NH), 3.50-3.55 (m, 2 H, CH_2N), 3.32-3.35 (m, 2 H, CH_2N), 3.19-3.25 (m, 2 H, CH_2N), 1.82-1.86 (m, 2 H, CH_2), 1.48 [s, 9 H, $C(CH_3)_3$], 1.12 (t, *J* = 7.0 Hz, 3 H, CH_3); ^{13}C NMR δ 159.0 (NCO_2), 156.2 (C-3), 148.9 (C-4a), 135.4 (C-6), 130.8 (C-8a), 126.4 (C-5), 124.6 (C-7), 120.4 (C-8), 79.6 [$\underline{C}(CH_3)_3$], 43.5 (CH_2N), 42.0 (CH_2N), 37.9 (CH_2N), 27.9 [$C(\underline{C}H_3)_3$], 27.4 (CH_2), 13.8 (CH_3); Anal. calc. for $C_{17}H_{25}N_5O_3$: C, 58.8; H, 7.3; N, 20.2; found C, 59.0; H, 7.3; N, 20.4%.

Example 53

3-{[2-(2-Hydroxyethoxy)ethyl]amino}-1,2,4-benzotriazine 1-oxide (33). A solution of chloride **19** (3.0 g, 16.5 mmol) in DCM (50 mL) was added to a stirred solution of 2-(aminoethoxy)ethanol (2.49 mL, 24.8 mmol) and Et_3N (3.45 mL, 24.8 mmol) in DCM (80 mL) and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue chromatographed, eluting with 40% EtOAc/DCM, to give 1-oxide **33** (2.62 g, 63%) as a yellow powder, mp (DCM/EtOAc) 131-131.5 °C; ^{1}H NMR δ 8.25 (dd, *J* = 8.7, 1.2 Hz, 1 H, H-8), 7.68 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1 H, H-6), 7.57 (d, *J* = 8.4 Hz, 1 H, H-5), 7.28 (ddd, *J* = 8.7, 7.2, 1.3 Hz, 1 H, H-7), 6.02 (br s, 1 H, NH), 3.74-3.80 (m, 6 H, 3 × CH_2O), 3.64-3.67 (m, 2 H, CH_2N), 2.71 (t, *J* = 5.9 Hz, 1 H, OH); ^{13}C NMR δ 158.9, 149.7, 135.5, 130.9, 126.4, 124.9, 120.4, 72.4, 69.5, 61.7, 41.9; Anal. calc. for $C_{11}H_{14}N_4O_3$: C, 52.8; H, 5.6; N, 22.4; found C, 52.9; H, 5.7; N, 22.6%.

Example 54

3-{[2-(2-Azidoethoxy)ethyl]amino}-1,2,4-benzotriazine 1-oxide (34). Methanesulfonyl chloride (0.82 mL, 10.6 mmol) was added dropwise to a stirred solution of alcohol **33** (2.41 g, 9.63 mmol) and Et_3N (1.74 mL, 12.5 mmol) in DCM (100 mL) at 5 °C and the solution stirred at 20 °C for 1 h. The solution was diluted with DCM (100 mL) and washed with water (3 × 50 mL), brine (50 mL), dried and the

solvent evaporated. The residue was dissolved in DMF (50 mL) and NaN_3 (0.69 g, 10.6 mmol) added. The mixture was heated at 100 °C for 2 h, cooled to 30 °C and the solvent evaporated. The residue was partitioned between EtOAc (100 mL) and water (100 mL). The organic fraction was washed with brine (50 mL), dried, and the solvent evaporated. The residue was chromatographed, eluting with 50% EtOAc/pet. ether, to give azide **34** (2.35 g, 89%) as yellow crystals, mp (EtOAc/pet. ether) 102-104 °C; ^{1}H NMR δ 8.27 (dd, *J* = 8.7, 1.4 Hz, 1 H, H-8), 7.70 (ddd, *J* = 8.6, 7.1, 1.5 Hz, 1 H, H-6), 7.59 (d, *J* = 8.6 Hz, 1 H, H-5), 7.29 (ddd, *J* = 8.6, 7.1, 1.4 Hz, 1 H, H-7), 5.70 (br s, 1 H, NH), 3.71-3.78 (m, 4 H, 2 × CH_2O), 3.69 (dd, *J* = 5.3, 4.8 Hz, 2 H, CH_2N_3), 3.41 (dd, *J* = 5.1, 4.9 Hz, 2 H, CH_2N); ^{13}C NMR δ 158.9, 148.7, 135.5, 131.1, 126.5, 125.0, 120.4, 70.0, 69.6, 50.7, 41.1; Anal. calc. for $C_{11}H_{13}N_7O_2$; C, 48.0; H, 4.8; N, 35.6; found: C, 48.3; H, 4.6; N, 35.7%.

Example 55

3-{[2-(2-*tert*-Butyloxycarbamoylethoxy)ethyl]amino}-1,2,4-benzotriazine 1-oxide (35). Propane-1,3-dithiol (5.7 mL, 57.0 mmol) was added dropwise to a stirred solution of azide **34** (1.57 g, 5.70 mmol) and Et_3N (7.95 mL, 57 mmol) in MeOH (100 mL) under N_2 and the solution heated at reflux temperature for 8 h. The solution was cooled to 30 °C and partitioned between 1 M HCl (100 mL) and Et_2O (100 mL). The aqueous fraction was adjusted to pH 12 with 7 M NaOH solution and extracted with DCM (3 × 50 mL). The organic fraction was dried and the solvent evaporated. The residue was dissolved in THF (100 mL) and a solution of di-*tert*-butyldicarbonate (1.87 g, 8.55 mmol) in THF (50 mL) added dropwise. The solution was stirred at 20 °C for 16 h, the solvent evaporated and the residue chromatographed, eluting with 40% EtOAc/pet. ether, to give carbamate **35** (1.85 g, 93%) as a yellow solid, mp (EtOAc/pet. ether) 134-137 °C; ^{1}H NMR δ 8.26 (dd, *J* = 8.4, 0.9 Hz, 1 H, H-8), 7.71 (ddd, *J* = 8.3, 7.1, 1.4 Hz, 1 H, H-6), 7.59 (d, *J* = 8.3 Hz, 1 H, H-5), 7.29 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1 H, H-7), 5.74 (br s, 1 H, NH), 4.93 (br s, 1 H, NH), 3.67-3.73 (m, 4 H, 2 × CH_2O), 3.56 (t, *J* = 5.2 Hz, 2 H, CH_2N), 3.29-3.36 (m, 2 H, CH_2N), 1.45 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 159.9, 155.9, 148.7, 135.5, 131.0, 126.5, 125.0, 120.4, 79.4, 70.2, 69.2, 41.1, 40.4, 28.4 (3); Anal. calc. for $C_{16}H_{23}N_5O_4$: C, 55.0; H, 6.6; N, 20.1; found C, 55.3; H, 6.8; N, 20.1%.

Example 56

***N*-[2-(2-Aminoethoxy)ethyl]-1,2,4-benzotriazin-3-amine 1-oxide (36).**

A solution of carbamate **35** (0.99 g, 2.8 mmol) in MeOH (30 mL) was treated with HCl gas and stirred at 20 °C for 2 h. The solvent was evaporated and the residue partioned between dilute NH_4OH (50 mL) and $CHCl_3$ (50 mL). The organic fraction was dried and the solvent evaporated to give amine **36** (618 mg, 88%) as a red solid, mp 116-118 °C; ^{1}H NMR δ 8.25 (dd, *J* = 8.7, 1.1 Hz, 1 H, H-8), 7.70 (ddd, *J* = 8.4, 7.1, 1.1 Hz, 1 H, H-6), 7.58 (d, *J* = 8.4 Hz, 1 H, H-5), 7.28 (ddd, *J* = 8.7, 7.1, 1.1 Hz, 1 H, H-7), 6.04 (br s, 1 H, NH), 3.68-3.76 (m, 4 H, 2 × CH_2O), 3.54 (t, *J* = 5.1 Hz, 2 H, CH_2N), 2.90 (t, *J* = 5.1 Hz, 2 H, CH_2N), 1.82 (br s, 2 H, NH_2); ^{13}C NMR δ 158.9 (C-3), 148.8 (C-4a), 135.5 (C-6), 130.9 (C-8a), 126.4 (C-5), 124.9 (C-7), 120.4 (C-8), 73.1 (CH_2O), 69.2 (CH_2O), 41.7 (CH_2N), 41.2 (CH_2N); Anal. calc. for $C_{25}H_{22}N_6O_3.½H_2O$: C, 51.15; H, 6.2; N, 27.1; found C, 51.6; H, 6.1; N, 26.8%.

Example 57

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(1-oxido-1,2,4-benzotriazin-3-yl)-1,2-ethanediamine (37).** *N,N*-Dimethylethanediamine (0.66 mL, 6.0 mmol) was added to a stirred solution of chloride **19** (438 mg, 2.4 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 2 h. The solution was cooled, the solvent evaporated and the residue partitioned between dilute aqueous NH_3 (100 mL) and DCM (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **37** (514 mg, 91%) as a yellow solid, mp (MeOH/EtOAc) 121-123 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.13 (dd, *J* = 8.6, 1.1 Hz, 1 H, H-8'), 7.78 (ddd, *J* = 8.5, 7.0, 1.1 Hz, 1 H, H-6'), 7.72 (br s, 1 H, NH), 7.57 (br d, *J* = 8.5 Hz, 1 H, H-5'), 7.33 (ddd, *J* = 8.6, 7.0, 1.3 Hz, 1 H, H-7'), 3.41-3.45 (m, 2 H, CH_2N), 2.45-2.50 (m, 2 H, CH_2N), 2.20 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR [$(CD_3)_2SO$] δ 158.8 (C-3'), 148.3 (C-4a'), 135.6 (C-6'), 129.9 (C-8a'), 125.9 (C-5'), 124.4 (C-7'), 119.8 (C-8'), 57.6 (CH_2N), 45.1 [$N(CH_3)_2$], 38.6 (CH_2N); Anal. calc. for $C_{11}H_{15}N_5O$; C, 56.6; H, 6.5; N, 30.0; found C, 56.8: H, 6.6; N, 30.4%.

Example 58

***N*^{1},*N*^{1},*N*^{2}-Trimethyl-*N*^{2}-(1-oxido-1,2,4-benzotriazin-3-yl)-1,2-ethanediamine (38).**

N^1,*N*^{1},*N*^{2}-Trimethyl-1,2-ethanediamine (0.45 mL, 3.5 mmol) was added to a stirred solution of chloride **19** (210 mg, 1.2 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 16 h. The solution was cooled, the solvent evaporated and the residue partitioned between dilute aqueous NH_3 (100 mL) and DCM (100 mL). The

organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **38** (277 mg, 96%) as a yellow solid which was recrystallized as the hydrochloride salt, mp (MeOH/EtOAc) 220-223 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.64 (br s, 1 H, NH^+Cl^-), 8.16 (dd, *J* = 8.7, 1.3 Hz, 1 H, H-8'), 7.84 (ddd, *J* = 8.6, 7.1, 1.3 Hz, 1 H, H-6'), 7.64 (d, *J* = 8.6 Hz, 1 H, H-5'), 7.40 (ddd, *J* = 8.7, 7.1, 1.2 Hz, 1 H, H-7'), 4.04 (t, *J* = 6.3 Hz, 2 H, CH_2N), 3.37-3.42 (m, 2 H, CH_2N), 3.21 (s, 3 H, NCH_3), 2.85 [d, *J* = 4.5 Hz, 6 H, $N(CH_3)_2$]; ^{13}C NMR [$(CD_3)_2SO$] δ 158.2 (C-3'), 148.1 (C-4a'), 136.0 (C-6'), 129.4 (C-8a'), 126.2 (C-5'), 125.3 (C-7'), 119.8 (C-8'), 53.5 (CH_2N), 43.7 (NCH_3), 42.5 [$N(CH_3)_2$], 35.0 (CH_2N); Anal. calc. for $C_{12}H_{18}ClN_5O$: C, 50.8; H, 6.4; N, 24.7; Cl, 12.5; found C, 51.3: H, 6.7; N, 24.8; Cl, 12.7%.

Example 59

***N*^{1}-(1-Oxido-1,2,4-benzotriazin-3-yl)-*N*^{2},*N*^{2}-dipropyl-1,2-ethanediamine hydrochloride (39).** MsCl (125 μL, 1.6 mmol) was added to a stirred solution of alcohol **22** (277 mg, 1.3 mmol) and Et_3N (280 μL, 2.0 mmol) in dry DCM (50 mL) at 5 °C and the solution stirred for 2 h at 20 °C. The solution was diluted with DCM (30 mL), washed with water (2 × 20 mL), the organic fraction dried and the solvent evaporated. The residue was dissolved in DMF (5 mL) and di-*n*-propylamine (9.2 mL, 67 mmol) added and the solution heated at 50 °C for 2 h. The solvent was evaporated and the residue partitioned between EtOAc (50 mL) and water (50 mL). The organic fraction was extracted with water (2 × 25 mL), dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (2-5%) of MeOH/DCM, to give the amine **39** (152 mg, 39 %) which was dissolved in HCl saturated MeOH, the solvent evaporated and the residue crystallized as a tan solid, mp (MeOH/EtOAc) 159-161 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.70 (br s, 1 H, NH^+Cl^-), 8.17 (dd, *J* = 8.6, 1.0 Hz, 1 H, H-8), 8.14 (br s, 1 H, NH), 7.84 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1 H, H-6'), 7.59 (d, *J* = 8.4 Hz, 1 H, H-5'), 7.40 (ddd, *J* = 8.6, 7.0, 1.3 Hz, 1 H, H-7'), 3.74-3.81 (m, 2 H, CH_2N), 3.29-3.33 (m, 2 H, CH_2N), 3.03-3.13 (m, 4 H, 2 × CH_2N), 1.70-1.79 (m, 4 H, 2 × CH_2), 0.93 (t, *J* = 7.3 Hz, 6 H, 2 × CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 158.5 (C-3'), 147.8 (C-4a'), 135.9 (C-6'), 130.3 (C-8a'), 126.0 (C-5'), 125.1 (C-7'), 119.8 (C-8'), 53.6 (2 × CH_2N), 50.1 (CH_2N), 35.3 (CH_2N), 16.3 (2 × CH_2), 10.8 (2 × CH_3); Anal. calc. for $C_{15}H_{23}N_5O.2HCl$; C, 49.7; H, 7.0; N, 19.3; Cl, 19.6; found C, 50.1; H, 7.0; N, 19.4; Cl, 19.4%.

Example 60

***N*-[2-(1-Pyrrolidinyl)ethyl]-1,2,4-benzotriazin-3-amine 1-oxide (40).** 2-(1-Pyrrolidinyl)ethylamine (1.25 mL, 9.9 mmol) was added to a stirred solution of chloride **19** (599 mg, 3.3 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 4 h. The solution was cooled, the solvent evaporated and the residue partitioned between dilute aqueous NH_3 (100 mL) and DCM (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **40** (806 mg, 94%) as a yellow solid, mp (DCM) 141-143 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.13 (dd, *J* = 8.6, 1.0 Hz, 1 H, H-8), 7.81 (br s, 1 H, NH), 7.78 (ddd, *J* = 8.4, 7.0, 1.0 Hz, 1 H, H-6), 7.57 (d, *J* = 8.4 Hz, 1 H, H-5), 7.33 (ddd, *J* = 8.6, 7.0, 1.0 Hz, 1 H, H-7), 3.42-3.48 (m, 2 H, CH_2N), 2.63 (t, *J* = 6.8 Hz, 2 H, CH_2N), 2.47-2.53 (m, 4 H, 2 × CH_2N), 1.64-1.71 (m, 4 H, 2 × CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 158.8 (C-3), 148.3 (C-4a), 135.6 (C-6), 128.0 (C-8a), 126.0 (C-5), 124.4 (C-7), 119.8 (C-8), 54.2 (CH_2N), 53.5 (2 × CH_2N), 39.8 (CH_2N), 23.0 (2 × CH_2); Anal. calc. for $C_{13}H_{17}N_5O$; C, 60.2; H, 6.6; N, 27.0; found C, 60.2: H, 6.9; N, 27.3%.

Example 61

***N*-[2-(4-Morpholinyl)ethyl]-1,2,4-benzotriazin-3-amine 1-oxide (41).** 2-(4-Morpholinyl)ethylamine (1.2 mL, 8.9 mmol) was added to a stirred solution of chloride **19** (541 mg, 3.0 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 4 h. The solution was cooled, the solvent evaporated and the residue partitioned between dilute aqueous NH_3 (100 mL) and DCM (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **41** (802 mg, 98%) as a yellow solid, mp (DCM) 170-172 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.13 (dd, *J* = 8.6, 1.2 Hz, 1 H, H-8), 7.79 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 1 H, H-6), 7.76 (br s, 1 H, NH), 7.57 (d, *J* = 8.4 Hz, 1 H, H-5), 7.34 (ddd, *J* = 8.6, 7.0, 1.2 Hz, 1 H, H-7), 3.55-3.58 (m, 4 H, 2 × CH_2O), 3.45-3.50 (m, 2 H, CH_2N), 2.51-2.56 (m, 2 H, CH_2N), 2.41-2.45 (m, 4 H, 2 × CH_2N); ^{13}C NMR [$(CD_3)_2SO$] δ 158.9 (C-3), 148.3 (C-4a), 135.7 (C-6), 130.0 (C-8a), 126.0 (C-5), 124.5 (C-7), 119.8 (C-8), 66.1 (2 × CH_2O), 56.8 (CH_2N), 53.2 (2 × CH_2N), 37.7 (CH_2N); Anal. calc. for $C_{13}H_{17}N_5O_2$: C, 56.7; H, 6.2; N, 25.4; found C, 56.5; H, 6.3; N, 25.1%.

Example 62

***N*-[2-(1- Piperidinyl)ethyl]-1,2,4-benzotriazin-3-amine 1-oxide (42)**. 2-(1-Piperidinyl)ethylamine (1.2 mL, 8.2 mmol) was added to a stirred solution of chloride **19** (499 mg, 2.7 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 1 h. The solution was cooled, the solvent evaporated and the residue partitioned between dilute aqueous NH_3 (100 mL) and DCM (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-4%) of MeOH/DCM, to give 1-oxide **42** (644 mg, 86%) as a yellow solid, mp (DCM) 141-144 °C; ^{1}H NMR δ 8.24 (d, *J* = 8.6, Hz, 1 H, H-8), 7.69 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1 H, H-6), 7.58 (d, *J* = 8.4 Hz, 1 H, H-5), 7.27 (ddd, *J* = 8.6, 7.0, 1.3 Hz, 1 H, H-7), 5.30 (br s, 1 H, NH), 3.57-3.64 (m, 2 H, CH_2N), 2.63-2.69 (m, 2 H, CH_2N), 2.47-2.54 (m, 4 H, 2 × CH_2N), 1.60-1.68 (m, 4 H, 2 × CH_2), 1.44-1.50 (m, 2 H, CH_2); ^{13}C NMR δ 158.8 (C-3), 148.9 (C-4a), 135.5 (C-6), 130.8 (C-8a), 126.4 (C-5), 124.7 (C-7), 120.5 (C-8), 56.8 (CH_2N), 54.3 (2 × CH_2N), 37.8 (CH_2N), 25.7 (2 × CH_2), 24.2 (CH_2); Anal. calc. for $C_{14}H_{19}N_5O$: C, 61.5; H, 7.0; N, 25.6; found C, 61.4: H, 7.1; N, 25.6%.

Example 63

***N*-[2-(2,6-Dimethyl-1-piperidinyl)ethyl]-1,2,4-benzotriazin-3-amine 1-oxide (43)**. 2-(2,6-Dimethyl-1-piperidinyl)ethylamine (636 mg, 4.1 mmol) was added to a stirred solution of chloride **19** (493 mg, 2.7 mmol) and Et_3N (0.57 mL, 4.1 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 2 h. The solution was cooled, the solvent evaporated and the residue partitioned between dilute aqueous NH_3 (100 mL) and DCM (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **43** (484 mg, 59%) as a yellow solid, mp (MeOH/DCM) 160-163 °C; ^{1}H NMR δ 8.25 (dd, *J* = 8.6, 1.4 Hz, 1 H, H-8), 7.68 (ddd, *J* = 8.5, 7.0, 1.4 Hz, 1 H, H-6), 7.57 (dd, *J* = 8.5, 1.3 Hz, 1 H, H-5), 7.27 (ddd, *J* = 8.6, 7.0, 1.3 Hz, 1 H, H-7), 5.68 (br s, 1 H, NH), 3.53-3.58 (m, 2 H, CH_2N), 2.91 (dd, *J* = 7.4, 7.1 Hz, 2 H, CH_2N), 2.50-2.59 (m, 2 H, 2 × CH), 1.65-1.70 (m, 1 H, CH_2), 1.54-1.59 (m, 2 H, CH_2), 1.35-1.40 (m, 1 H, CH_2), 1.25-1.33 (m, 2 H, CH_2), 1.20 (d, *J* = 6.3 Hz, 6 H, 2 × CH_3); ^{13}C NMR δ 159.0 (C-3), 148.9 (C-4a), 135.4 (C-6), 130.9 (C-8a), 126.5 (C-5), 124.7 (C-7), 120.5 (C-8), 57.3 (2 × CH), 47.4 (CH_2N), 39.5 (CH_2N), 34.2 (CH_2), 24.4 (2 × CH_2), 21.6 (2 × CH_3); Anal. calc. for $C_{16}H_{23}N_5O$: C, 63.8; H, 7.7; N, 23.2; found C, 63.6; H, 7.6; N, 23.3%.

Exampl 64

***N*^{1}-(1-Oxido-1,2,4-benzotriazin-3-yl)-*N*^{3},*N*^{3}-dimethyl-1,3-propanediamine (44).** N,N-dimethylpropylenediamine (0.9 mL, 6.9 mmol) was added dropwise to a stirred solution of chloride **19** (500 mg, 2.75 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 8 h. The solution was cooled to 20 °C, the solvent evaporated and the residue partitioned between aqueous NH_4OH solution (100 mL) and EtOAc (100 mL). The organic fraction was dried, and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **44** (629 mg, 92%) as a yellow solid, mp 137-138 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.13 (dd, *J* = 8.6, 1.1 Hz, 1 H, H-8'), 7.92 (br s, 1 H, NH), 7.77 (ddd, *J* = 8.4, 7.1, 1.1 Hz, 1 H, H-6'), 7.56 (d, *J* = 8.4 Hz, 1 H, H-5'), 7.32 (ddd, *J* = 8.6, 7.1, 1.1 Hz, 1 H, H-7'), 3.37 (br s, 2 H, H-1), 2.30 (t, *J* = 7.0 Hz, 2 H, H-3), 2.15 [s, 6 H, $N(CH_3)_2$], 1.70-1.76 (m, 2 H, H-2); ^{13}C NMR [$(CD_3)_2SO$] δ 158.8 (C-3'), 148.3 (C-4a'), 135.6 (C-6'), 129.9 (C-8a'), 125.9 (C-5'), 124.3 (C-7'), 119.8 (C-8'), 56.6 (CH_2N), 45.1 [$N(CH_3)_2$], 39.0 (CH_2N), 26.3 (CH_2); Anal. calc. for $C_{12}H_{17}N_5O$: C, 58.3; H, 6.9; N, 28.3; found C, 58.3; H, 7.0; N, 28.5%.

Example 65

***N*-Phenyl-1,2,4-benzotriazin-3-amine 1-oxide (45).** Two drops of cHCl were added to a solution of chloride **19** (0.52 g, 2.86 mmol) and aniline (0.78 mL, 8.59 mmol) in DME (10 mL) and the solution stirred at reflux temperature for 16 h. The solvent was evaporated and the residue chromatographed, eluting with 10% EtOAc/pet. ether, to give 1-oxide **45** (334 mg, 49%) as a yellow powder, mp 197-198.5 °C [lit. (Pazdera & Potacek, *Chem. Papers*, **1989**, *43*, 107) mp 199-201 °C]; ^{1}H NMR δ 8.32 (d, *J* = 9.0 Hz, 1 H, H-8), 7.70-7.77 (m, 4 H, H-5, H-6, H-2', H-6'), 7.37-7.42 (m, 3 H, H-7, H-3', H-5'), 7.22 (br s, 1 H, NH), 7.13 (dt, *J* = 7.5, 0.9 Hz, 1 H, H-4'); ^{13}C NMR δ 156.3 (C-3), 148.1 (C-4a), 138.1 (C-1'), 135.8 (C-6), 131.6 (C-8a), 129.1 (C-3', C-5'), 127.1 (C-5), 126.1 (C-4'), 123.8 (C-7), 120.4 (C-8), 119.7 (C-2', C-6').

Example 66

***N*-[3-(2-Methoxyethyl)phenyl]-1,2,4-benzotriazin-3-amine 1-oxide (49).**

1-(2-Methoxyethyl)-3-nitrobenzene (47). A solution of 3-nitrophenethyl alcohol (**46**) (1.05 g, 6.3 mmol) in THF (10 mL) was addded dropwise to a stirred suspension of NaH (325 mg, 8.1 mmol) in THF (30 mL) at 5 °C and the mixture warmed to 20 °C and stirred 30 min. Iodomethane (3.9 mL, 62.5 mmol) was added and the mixture stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned

between EtOAc (100 mL) and water (100 mL). The organic fraction was washed with water (2 × 30 mL), brine (30 mL), dried, and the solvent evaporated. The residue was chromatographed, eluting with 20% EtOAc/pet. ether, to give ether **47** (981 mg, 87%) as a clear oil, (Norman & Radda, *J. Chem. Soc.* **1961**, 3030) ^{1}H NMR δ 8.06-8.11 (m, 2 H, H-2, H-4), 7.57 (d, *J* = 7.6 Hz, 1 H, H-6), 7.47 (dd, *J* = 7.9, 7.6 Hz, 1 H, H-5), 3.65 (t, *J* = 6.5 Hz, 2 H, CH_2O), 3.36 (s, 3 H, OCH_3), 2.98 (t, *J* = 6.5 Hz, 2 H, CH_2); ^{13}C NMR δ 148.3 (C-3), 141.3 (C-1), 135.2 (C-6), 129.2 (C-5), 123.7 (C-2), 121.4 (C-4), 72.5 (CH_2O), 58.8 (OCH_3), 35.8 (CH_2).

3-(2-Methoxyethyl)aniline (48). A solution of ether **47** (928 mg, 5.1 mmol) in EtOH (50 mL) with Pd/C (100 mg) was stirred under H_2 (60 psi) for 2 h. The mixture was filtered through celite, washed with EtOH (2 × 10 mL) and the solvent evaporated to give aniline **48** (718 mg, 93%) as a pale pink oil, ^{1}H NMR δ 7.08 (dd, *J* = 7.7, 7.3 Hz, 1 H, H-5), 6.62 (br d, *J* = 7.3 Hz, 1 H, H-4), 6.51-6.55 (m, 2 H, H-2, H-6), 3.50 (br s, 2 H, NH_2), 3.58 (t, *J* = 7.2 Hz, 2 H, CH_2O), 3.35 (s, 3 H, OCH_3), 2.80 (t, *J* = 7.2 Hz, 2 H, CH_2); ^{13}C NMR δ 146.4 (C-1), 140.1 (C-3), 129.3 (C-5), 119.1 (C-4), 115.7 (C-2), 113.1 (C-6), 73.6 (CH_2O), 58.6 (OCH_3), 36.2 (CH_2); MS (EI$^+$) *m/z* 151 (M^+, 90%), 136 (20), 106 (100); HRMS (EI$^+$) calc. for $C_9H_{13}NO$ (M^+) *m/z* 151.0997, found 151.0995.

N-[3-(2-Methoxyethyl)phenyl]-1,2,4-benzotriazin-3-amine 1-oxide (49). A solution of chloride **19** (376 mg, 2.07 mmol) and aniline **48** (688 mg, 4.55 mmol) in DMSO (20 mL) was heated at 100 °C for 16 h. The solution was partitioned between EtOAc (100 mL) and water (100 mL), the organic fraction washed with water (2 × 50 mL), brine (50 mL), dried , and the solvent evaporated. The residue was chromatographed, eluting with a gradient (20-50%) of EtOAc/pet. ether, to give 1-oxide **49** (590 mg, 96%) as an orange powder, mp (EtOAc/Et_2O) 122-124 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.18 (s, 1 H, NH), 8.22 (dd, *J* = 8.6, 1.0 Hz, 1 H, H-8), 7.87 (ddd, *J* = 8.5, 7.1, 1.3 Hz, 1 H, H-6), 7.70-7.76 (m, 3 H, H-5, H-2', H-6'), 7.47 (ddd, *J* = 8.6, 7.1, 1.3 Hz, 1 H, H-7), 7.27 (dd, *J* = 7.9, 7.8 Hz, 1 H, H-5'), 6.94 (d, *J* = 7.8 Hz, 1 H, H-4'), 3.58 (t, *J* = 6.8 Hz, 2 H, CH_2O), 3.27 (s, 3 H, OCH_3), 2.82 (t, *J* = 6.8 Hz, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 156.3 (C-3'), 147.5 (C-3), 139.5 (C-1'), 139.1 (C-4a), 135.9 (C-6), 130.9 (C-8a), 128.4 (C-5'), 126.6 (C-5), 125.8 (C-4'), 123.2 (C-7), 119.8 (C-8), 119.7 (C-2'), 117.3 (C-6'), 72.6 (CH_2O), 57.8 (OCH_3), 35.5 (CH_2); Anal. calc. for $C_{16}H_{16}N_4O_2$: C, 64.9; H, 5.4; N, 18.9; found C, 65.0; H, 5.5; N, 19.2%.

Example 67

Methyl {4-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]phenyl}acetate (51). A solution of chloride **19** (992 mg, 5.5 mmol) and aniline **50** (1.99 g, 12.0 mmol) in DMSO (30 mL) was heated at 100 °C for 6 h and then 20 °C for 16 h. The solution was partitioned between EtOAc (200 mL) and water (200 mL), the organic fraction washed with water (2 × 100 mL), dried, and the solvent evaporated. The residue was chromatographed, eluting with 10% EtOAc/DCM, to give the 1-oxide **51** (1.05 g, 61%) as a yellow solid, mp (EtOAc/DCM) 216-218 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.00 (s, 1 H, NH), 8.24 (d, *J* = 8.3 Hz, 1 H, H-8"), 7.82 (d, *J* = 8.4 Hz, 2 H, H-2', H-6'), 7.79 (dd, *J* = 8.2, 7.3 Hz, 1 H, H-6"), 7.70 (d, *J* = 8.2 Hz, 1 H, H-5"), 7.40 (dd, *J* = 8.3, 7.3 Hz, 1 H, H-7"), 7.22 (d, *J* = 8.4 Hz, 2 H, H-3', H-5'), 3.67 (s, 3 H, OCH_3), 3.60 (s, 2 H, H-2); ^{13}C NMR [$(CD_3)_2SO$] δ 171.7 (C-1), 156.3 (C-3"), 147.9 (C-4a"), 138.1 (C-4'), 135.6 (C-6"), 131.9 (C-8a"), 129.4 (C-2', C-6'), 128.3 (C-1'), 126.7 (C-5"), 125.5 (C-7"), 119.9 (C-8"), 119.7 (C-3', C-5'), 51.7 (OCH_3), 40.1 (C-2); Anal. calc. for $C_{16}H_{14}N_4O_3$: C, 61.9; H, 4.6; N, 18.1; found C, 62.3; H, 4.8; N, 18.1%.

Example 68

{4-[(1-Oxido-1,2,4-benzotriazin-3-yl)amino]phenyl}acetic acid (52). A solution of NaOH (1 M, 5.2 mL, 5.2 mmol) was added to a stirred suspension of ester **51** (323 mg, 1.0 mmol) in MeOH (30 mL) and the mixture stirred at 20 °C for 2 h. The volume was reduced to ca. 10 mL and the remaining solution washed with Et_2O (2 × 10 mL). The solution was adjusted to pH 1 with 2 M HCl and the suspension extracted with EtOAc (3 × 50 mL), the combined organic fraction dried, and the solvent evaporated. Recrystallization gave the acid **52** (306 mg, 99%) as a yellow powder, mp (EtOAc) 243-245 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.27 (s, 1 H, CO_2H), 10.21 (s, 1 H, NH), 8.22 (dd, *J* = 8.6, 0.8 Hz, 1 H, H-8"), 7.88 (ddd, *J* = 8.4, 7.1, 1.0 Hz, 1 H, H-6"), 7.79 (d, *J* = 8.5 Hz, 2 H, H-2', H-6'), 7.75 (d, *J* = 8.4 Hz, 1 H, H-5"), 7.46 (ddd, *J* = 8.6, 7.1, 1.0 Hz, 1 H, H-7"), 7.25 (d, *J* = 8.5 Hz, 2 H, H-3', H-5'), 3.54 (s, 2 H, H-2); ^{13}C NMR [$(CD_3)_2SO$] δ 172.7 (C-1), 156.3 (C-3"), 147.6 (C-4a"), 137.7 (C-4'), 135.9 (C-6"), 130.9 (C-8a"), 129.5 (C-2', C-6'), 129.2 (C-1'), 126.5 (C-5"), 125.8 (C-7"), 119.8 (C-8"), 119.3 (C-3', C-5'), 40.0 (C-2); Anal. calc. for $C_{15}H_{12}N_4O_3$: C, 60.8; H, 4.1; N, 18.9; found C, 61.0; H, 4.0; N, 19.1%.

Example 69

2-{4-[(1-Oxido-1,2,4-benzotriazin-3-yl)amino]ph nyl}-N-(2-methoxyethyl)acetamide (53). A solution of acid **52** (259 mg, 0.87 mmol) and CDI (213 mg, 1.3 mmol) in DMF (10 mL) was stirred at 50 °C for 10 min. 2-Methoxyethylamine (152 μL, 1.75 mmol) was added dropwise and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in water (100 mL). The precipitate was filtered, dried, and recrystallized from MeOH to give amide **53** (239 mg, 78%) as a yellow powder, mp (MeOH) 216-218 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.19 (s, 1 H, NH), 8.21 (dd, *J* = 8.6, 1.0 Hz, 1 H, H-8"), 8.09 (dd, *J* = 5.6, 5.3 Hz, 1 H, CONH), 7.88 (ddd, *J* = 8.3, 7.1, 1.0 Hz, 1 H, H-6"), 7.73-7.78 (m, 3 H, H-2', H-6', H-5"), 7.47 (ddd, *J* = 8.6, 7.1, 1.0 Hz, 1 H, H-7"), 7.25 (d, *J* = 8.5 Hz, 2 H, H-3', H-5'), 3.40 (br s, 2 H, H-2), 3.32-3.37 (m, 2 H, CH_2O), 3.25 (s, 3 H, OCH_3), 3.23 (q, *J* = 5.7 Hz, 2 H, CH_2N); ^{13}C NMR [$(CD_3)_2SO$] δ 170.3 (C-1), 156.4 (C-3"), 147.6 (C-4a"), 137.5 (C-4'), 135.9 (C-6"), 130.9 (C-8a"), 130.7 (C-1'), 129.1 (C-2', C-6'), 128.5 (C-5"), 125.8 (C-7"), 119.8 (C-8"), 119.4 (C-3', C-5'), 70.6 (CH_2O), 57.8 (OCH_3), 41.6 (CH_2N), 38.4 (C-2); Anal. calc. for $C_{18}H_{19}N_5O_3$: C, 61.2; H, 5.4; N, 19.8; found C, 61.6; H, 5.3; N, 19.9%.

Example 70

***N*-[2-(Dimethylamino)ethyl]-2-{4-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]phenyl}acetamide (54)**. A solution of acid **52** (476 mg, 1.6 mmol) and CDI (391 mg, 2.4 mmol) in DMF (10 mL) was stirred at 50 °C for 10 min. *N*,*N*-Dimethylaminoethylamine (353 μL, 3.2 mmol) was added dropwise and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in EtOAc (200 mL). The precipitate was filtered and dried. The mother liquor was evaporated and the residue suspended in water (50 mL), the precipitate filtered, and combined with the previous crop to give amide **54** (562 mg, 95%) as a yellow powder, mp (EtOAc) 225-226 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.18 (s, 1 H, NH), 8.22 (dd, *J* = 8.6, 1.0 Hz, 1 H, H-8"), 7.92 (t, *J* = 5.4 Hz, 1 H, CONH), 7.87 (ddd, *J* = 8.4, 7.1, 1.0 Hz, 1 H, H-6"), 7.72-7.78 (m, 3 H, H-2', H-6', H-5"), 7.46 (ddd, *J* = 8.6, 7.1, 1.0 Hz, 1 H, H-7"), 7.24 (d, *J* = 8.5 Hz, 2 H, H-3', H-5'), 3.16 (dt, *J* = 6.7, 5.4 Hz, 2 H, CH_2N), 2.28 (t, *J* = 6.7 Hz, 2 H, CH_2N), 2.15 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR [$(CD_3)_2SO$) δ 170.1 (C-1), 156.4 (C-3"), 147.6 (C-4a"), 137.5 (C-4'), 135.7 (C-6"), 130.9 (C-8a"), 130.8 (C-1'), 129.1 (C-2', C-6'), 128.5 (C-5"), 125.8 (C-7"), 119.8 (C-8"), 119.4 (C-3', C-5'), 58.2 (CH_2N), 45.1 [$N(CH_3)_2$], 41.7 (CH_2N), 36.8 (C-2); Anal. calc. for $C_{19}H_{22}N_6O_2$: C, 62.3; H, 6.1; N, 22.9; found C, 62.6; H, 6.2; N, 22.7%.

Exampl 71

3-Methyl-1,2,4-benzotriazine 1-oxide (55). $Pd(PPh_3)_4$ (82 mg, 71 μmol) was added to a stirred, degassed solution of chloride **19** (258 mg, 1.42 mmol) and Me_4Sn (0.39 mL, 2.8 mmol) in DME (20 mL) and the solution stirred under N_2 at reflux temperature for 48 h. The solvent was evaporated and the residue chromatographed, eluting with 20% EtOAc/pet. ether, to give an oil which was chromatographed, eluting with 5% EtOAc/DCM, to give (i) starting material **19** (164 mg, 64%) and (ii) 1-oxide **55** (55 mg, 24%) as a white solid, mp (EtOAc/pet. ether) 99-101 °C [lit. (Atallah & Nazar, *Tetrahedron Lett.*, **1982**, *38*, 1793) mp (benzene/pet.ether) 101-102 °C]; ^1H NMR δ 8.44 (d, *J* = 8.6 Hz, 1 H, H-8), 7.90-7.97 (m, 2 H, H-5, H-6), 7.70 (ddd, *J* = 8.6, 6.8, 1.8 Hz, 1 H, H-7), 2.80 (s, 3 H, CH_3).

Example 72

3-Ethyl-1,2,4-benzotriazine 1-oxide (56). $Pd(PPh_3)_4$ (340 mg, 0.30 mmol) was added to a stirred, degassed solution of chloride **19** (539 mg, 2.97 mmol) and Et_4Sn (0.54 mL, 2.7 mmol) in DME (20 mL) and the solution stirred under N_2 at reflux temperature for 4 h. The solvent was evaporated and the residue chromatographed, eluting with 20% EtOAc/pet. Ether, to give an oil which was chromatographed, eluting with 5% EtOAc/DCM, to give 1-oxide **56** (448 mg, 86%) as a white solid, mp (EtOAc/pet. ether) 78-80 °C; ^1H NMR δ 8.45 (dd, *J* = 8.7, 1.1 Hz, 1 H, H-8), 7.99 (dd, *J* = 8.5, 1.1 Hz, 1 H, H-5), 7.93 (ddd, *J* = 8.5, 7.1, 1.3 Hz, 1 H, H-6), 7.69 (ddd, *J* = 8.7, 7.1, 1.2 Hz, 1 H, H-7), 3.06 (q, *J* = 7.6 Hz, 2 H, CH_2), 1.45 (t, *J* = 7.6 Hz, 3 H, CH_3); ^{13}C NMR δ 168.1 (C-3), 147.6 (C-4a), 135.5 (C-6), 133.2 (C-8a), 129.8 (C-5), 128.7 (C-7), 120.1 (C-8), 30.7 (CH_2), 12.2 (CH_3); Anal. calc. for $C_9H_9N_3O_3$: C, 61.7; H, 5.2; N, 24.0; found C, 62.0; H, 5.0; N, 24.6%.

Example 73

3-Phenyl-1,2,4-benzotriazine 1-oxide (57). $Pd(PPh_3)_4$ (314 mg, 0.27 mmol) was added to a stirred, degassed solution of chloride **19** (986 mg, 5.43 mmol) and phenylboronic acid (0.73 g, 5.97 mmol) in DME (50 mL) and Cs_2CO_3 (5.3 g, 16.3 mmol) in water (10 mL) and the mixture stirred under N_2 at reflux temperature for 2 h. The mixture was partitioned between EtOAc (100 mL) and water (100 mL), the organic fraction washed with water (2 × 50 mL), dried, and the solvent was evaporated. The residue was chromatographed, eluting with a gradient (20-50%) of EtOAc/pet. ether, to give an oil which was chromatographed, eluting with 5%

EtOAc/DCM, to give 1-oxide **57** (743 mg, 61%) as a white solid, mp (EtOAc/pet. ether) 125-127 °C; ^{1}H NMR δ 8.49-8.54 (m, 3 H, H-8, H-2', H-6'), 8.09 (d, *J* = 8.6 Hz, 1 H, H-5), 7.94 (ddd, *J* = 8.6, 7.1, 1.4 Hz, 1 H, H-6), 7.70 (ddd, *J* = 8.7, 7.1, 1.4 Hz, 1 H, H-7), 7.51-7.57 (m, 3 H, H-3', H-4', H-5'); ^{13}C NMR δ 160.7 (C-3), 147.7 (C-4a), 135.6 (C-6), 134.1 (C-1'), 133.5 (C-8a), 131.9 (C-5), 130.5 (C-7), 129.4 (C-4'), 128.8 (C-2', C-6'), 128.5 (C-3', C-5'), 120.3 (C-8); Anal. calc. for $C_{13}H_9N_3O$: C, 69.9; H, 4.1; N, 18.8; found C, 69.9; H, 4.0; N, 18.7%.

Example 74

3-(4-Methoxyphenyl)-1,2,4-benzotriazine 1-oxide (58). $Pd(PPh_3)_4$ (162 mg, 0.14 mmol) was added to a stirred, degassed solution of chloride **19** (510 mg, 2.8 mmol) and 4-methoxyphenylboronic acid (0.47 g, 3.1 mmol) in DME (50 mL) and Cs_2CO_3 (3.0 g, 8.4 mmol) in water (8 mL) and the mixture stirred under N_2 at reflux temperature for 2 h. The mixture was partitioned between EtOAc (100 mL) and water (100 mL), the organic fraction washed with water (2 × 50 mL), dried, and the solvent was evaporated. The residue was chromatographed, eluting with a gradient (20-50%) of EtOAc/pet. ether, to give an oil which was chromatographed, eluting with 5% EtOAc/DCM, to give 1-oxide **58** (408 mg, 57%) as a white solid, mp (EtOAc/pet. ether) 168-170 °C; ^{1}H NMR δ 8.44-8.49 (m, 3 H, H-8, H-2', H-6'), 8.02 (d, *J* = 8.7 Hz, 1 H, H-5), 7.90 (ddd, *J* = 8.7, 7.2, 1.4 Hz, 1 H, H-6), 7.64 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1 H, H-7), 7.02 (ddd, *J* = 9.0, 2.9, 2.1 Hz, 2 H, H-3', H-5'), 3.90 (s, 3 H, OCH_3); ^{13}C NMR δ 162.8 (C-4'), 160.5 (C-3), 147.8 (C-4a), 135.5 (C-6), 133.2 (C-8a), 130.3 (C-3', C5'), 129.5 (C-5), 129.1 (C-7), 126.5 (C-1'), 120.3 (C-8), 114.3 (C-2', C-6'), 55.4 (OCH_3); Anal. calc. for $C_{14}H_{11}N_3O_2$: C, 66.4; H, 4.4; N, 16.6; found C, 66.5; H, 4.4; N, 16.7%.

Example 75

3-Vinyl-1,2,4-benzotriazine 1-oxide (59). $Pd(PPh_3)_4$ (204 mg, 0.18 mmol) was added to a stirred solution of chloride **19** (320 mg, 1.8 mmol) and vinyltributyltin (0.77 mL, 2.6 mmol) in DME (20 mL), the solution degassed and stirred under N_2 at reflux temperature for 6 h. The solvent was evaporated and the residue chromatographed, eluting with 20% EtOAc/pet. ether to give an oil which was chromatographed, eluting with 5% EtOAc/DCM, to give 1-oxide **59** (177 mg, 58%) as a white solid, mp (EtOAc/pet. ether) 85-86 °C; ^{1}H NMR δ 8.46 (dd, *J* = 8.9, 1.4 Hz, 1 H, H-8), 8.10 (d, *J* = 8.5 Hz, 1 H, H-5), 7.92 (ddd, *J* = 8.5, 7.1, 1.4 Hz, 1 H, H-6), 7.69 (ddd, *J* = 8.9, 7.1, 1.4 Hz, 1 H, H-7), 6.86 (dd, *J* = 17.4, 9.4 Hz, 2 H, H-1'), 6.79 (dd, *J* = 17.4, 2.2 Hz, 1

H, H-2'), 5.92 (dd, J = 9.4, 2.2 Hz, 1 H, H-2'); ^{13}C NMR δ 160.2 (C-3), 147.4 (C-4a), 135.6 (C-6), 133.6 (C-8a), 133.0 (C-2'), 130.2 (C-5), 129.1 (C-7), 126.6 (C-1'), 120.2 (C-8); Anal. calc. for $C_9H_7N_3O$: C, 62.4; H, 4.1; N, 24.3; found C, 61.8; H, 4.0; N, 24.4%.

Example 76

3-Allyl-1,2,4-benzotriazine 1-oxide (60). $Pd(PPh_3)_4$ (340 mg, 0.29 mmol) was added to a stirred solution of chloride **19** (1.1 g, 5.9 mmol) and allyltributyltin (2.0 mL, 6.5 mmol) in DME (60 mL), the solution degassed and stirred under N_2 at reflux temperature for 6 h. The solvent was evaporated and the residue chromatographed, eluting with 20% EtOAc/pet. ether, to give an oil which was chromatographed, eluting with 5% EtOAc/DCM, to give 1-oxide **60** (1.00 g, 90%) as a white solid, mp (EtOAc/pet. ether) 57-58 °C; ^{1}H NMR δ 8.45 (dd, J = 8.6, 1.4 Hz, 1 H, H-8), 8.10 (dd, J = 8.4, 1.4 Hz, 1 H, H-5), 7.94 (ddd, J = 8.4, 7.1, 1.4 Hz, 1 H, H-6), 7.70 (ddd, J = 8.6, 7.1, 1.4 Hz, 1 H, H-7), 6.15-6.24 (m, 1 H, H-2'), 5.31 (dq, J = 17.0, 1.5 Hz, 1 H, H-3'), 5.24 (dq, J = 10.1, 1.5 Hz, 1 H, H-3'), 3.80 (dq, J = 6.8, 1.5 Hz, 2 H, H-1'); ^{13}C NMR δ 165.2 (C-3), 147.5 (C-4a), 135.6 (C-6), 133.3 (C-8a), 132.7 (C-2'), 130.1 (C-5), 128.8 (C-7), 120.8 (C-8), 118.5 (C-3'), 41.8 (C-1'); Anal. calc. for $C_{10}H_9N_3O$: C, 64.2; H, 4.9; N, 22.5; found C, 63.9; H, 4.9; N, 22.7%.

Example 77

3-(2-Hydroxyethyl)-1,2,4-benzotriazine 1-oxide (61). Ozone was bubbled into a solution of **60** (548 mg, 2.9 mmol) in DCM/MeOH (1:1, 50 mL) at –78 °C until a blue colour persisted. The solution was purged with N_2 to remove excess ozone and a solution of $NaBH_4$ (111 mg, 2.9 mmol) in EtOH (10 mL) added dropwise and the solution allowed to warm to 20 °C over 1 h. HOAc (1 mL) was added and the solution stirred at 20 °C for 30 min. The solvent was evaporated and the residue partitioned between DCM (50 mL) and water (3 × 50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with 50% EtOAc/pet. ether, to give alcohol **61** (392 mg, 70%) as pale yellow needles, mp 105-107 °C; ^{1}H NMR δ 8.45 (dd, J = 8.6, 1.3 Hz, 1 H, H-8), 7.99 (dd, J = 8.5, 1.6 Hz, 1 H, H-5), 7.96 (ddd, J = 8.5, 6.7, 1.3 Hz, 1 H, H-6), 7.72 (ddd, J = 8.5, 6.7, 1.6 Hz, 1 H, H-7), 4.18-4.20 (m, 2 H, CH_2O), 3.29 (t, J = 5.6 Hz, 2 H, CH_2), 3.11 (t, J = 5.5 Hz, 1 H, OH); ^{13}C NMR δ 165.4 (C-3), 147.0 (C-4a), 135.8 (C-6), 133.6 (C-8a), 130.2 (C-5), 128.6 (C-7), 120.1 (C-8), 60.0 (CH_2O), 39.0 (CH_2); Anal. calc. for $C_9H_9N_3O_2$: C, 56.5; H, 4.7; N, 22.0; found C, 56.8; H, 4.7; N, 21.8%.

Example 78

3-(2-Oxiranylmethyl)-1,2,4-benzotriazine 1-oxide (62). MCPBA (0.96 g, 3.9 mmol) was added to a stirred solution of alkene **60** (484 mg, 2.6 mmol) in DCM (50 mL) at 20 °C and the mixture stirred for 16 h. The solution was diluted with DCM (100 mL), washed with dilute aqeous NH_3 (3 × 50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with 50% EtOAc/pet. ether, to give (i) starting material **60** (173 mg, 36%) and (ii) epoxide **62** (251 mg, 48%) as white crystals, mp (EtOAc/pet. ether) 105-107 °C; ^{1}H NMR δ 8.46 (dd, *J* = 8.7, 1.2 Hz, 1 H, H-8), 8.03 (dd, *J* = 8.5, 1.1 Hz, 1 H, H-5), 7.95 (ddd, *J* = 8.5, 7.1, 1.2 Hz, 1 H, H-6), 7.73 (ddd, *J* = 8.7, 7.1, 1.1 Hz, 1 H, H-7), 3.55-3.60 (m, 1 H, H-2'), 3.27 (dd, *J* = 5.8, 1.9 Hz, 2 H, H-1'), 2.93 (dd, *J* = 4.7, 4.1 Hz, 1 H, H-3'), 2.76 (dd, *J* = 4.7, 2.6 Hz, 1 H, H-3'); ^{13}C NMR δ 163.4 (C-3), 147.4 (C-4a), 135.7 (C-6), 133.6 (C-8a), 130.4 (C-5), 128.9 (C-7), 120.1 (C-8), 50.0 (C-2'), 47.1 (C-3'), 40.5 (C-1'); Anal. calc. for $C_{10}H_9N_3O_2$: C, 59.1; H, 4.5; N, 20.7; found C, 59.2; H, 4.6; N, 20.4%.

Example 79

3-(2-Methoxyethyl)-1,2,4-benzotriazine 1-oxide (63). Five aliquots of $TMSCH_2N_2$ (3 mL, 6.0 mmol) were added to a stirred solution of alcohol **61** (1.14 g, 6.0 mmol) and HBF_4 (1.5 mL, 12 mmol) in DCM (50 mL) over 3 h. The solution was stirred at 20 °C for 16 h, the solvent evaporated and the residue chromatographed, eluting with 30% EtOAc/pet. ether, to give (i) methyl ether **63** (375 mg, 30%) as a yellow powder, mp (EtOAC/pet. ether) 56-58 °C; ^{1}H NMR δ 8.45 (dd, *J* = 8.7, 1.2, 1 H, H-8), 8.03 (d, *J* = 8.4 Hz, 1 H, H-5), 7.92 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 1 H, H-6), 7.71 (ddd, *J* = 8.7, 7.0, 1.1 Hz, 1 H, H-7), 3.97 (dd, *J* = 6.5, 6.3 Hz, 2 H, CH_2O), 3.38 (s, 3 H, OCH_3), 3.31 (dd, *J* = 6.5, 6.3 Hz, 2 H, CH_2); ^{13}C NMR δ 164.7 (C-3), 147.3 (C-4a), 135.6 (C-6), 130.3 (C-8a), 130.1 (C-5), 128.7 (C-7), 120.1 (C-8), 70.0 (CH_2O), 58.8 (OCH_3), 37.6 (CH_2); Anal. calc. for $C_{10}H_{11}N_3O_2$: C, 58.5; H, 5.4; N, 20.5; found: C, 58.8; H, 5.4; N, 20.6%; and (ii) starting material **61** (334 mg, 24%), spectroscopically identical to sample prepared above.

Example 80

2-(1-Oxido-1,2,4-benzotriazin-3-yl)-*N*,*N*-dimethylethanamine (64). MsCl (246 μL, 3.1 mmol) was added to a stirred solution of alcohol **61** (496 mg, 2.6 mmol) and Et_3N (470 μL, 3.4 mmol) in dry DCM (50 mL) at 20 °C and the solution stirred for 2 h. The solution was diluted with DCM (50 mL), washed with water (2 × 10 mL), brine (20

mL), the organic fraction dried and the solvent evaporated. The residue was dissolved in THF (50 mL) and Et_3N (9.0 mL, 64.9 mmol) and dimethylamine hydrochloride (5.3 g, 64.9 mmol) added and the solution heated at reflux temperature for 3 h, then stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between EtOAc (100 mL) and water (100 mL). The organic fraction was extracted with water (2 × 25 mL), dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-20%) of MeOH/EtOAc then 1% Et_3N/20% MeOH/EtOAc, to give amine **64** (528 mg, 93%) as a yellow/orange solid, mp (MeOH/EtOAc) 47-49 °C, ^{1}H NMR [$(CD_3)_2SO$] δ 8.36 (d, *J* = 8.5 Hz, 1 H, H-8'), 8.02-8.10 (m, 2 H, H-5', H-6'), 7.83 (ddd, *J* = 8.5, 6.7, 1.6 Hz, 1 H, H-7'), 3.09 (dd, *J* = 7.5, 7.2 Hz, 2 H, H-1), 2.81 (d, *J* = 7.5, 7.2 Hz, 2 H, H-2), 2.22 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR [$(CD_3)_2SO$] δ 165.1 (C-3'), 146.8 (C-4a'), 136.1 (C-6'), 132.7 (C-8a'), 130.5 (C-5'), 128.3 (C-7'), 119.5 (C-8'), 56.9 (C-1), 44.7 [$N(CH_3)_2$], 34.6 (C-1); Anal. calc. for $C_{11}H_{14}N_4O$: C, 60.5; H, 6.5; N, 25.7; found C, 60.7; H, 6.7; N, 25.6%.

Example 81

3-[2-(4-Morpholinyl)ethyl]-1,2,4-benzotriazine 1-oxide hydrochloride (65). MsCl (381 μL, 4.8 mmol) was added to a stirred solution of alcohol **61** (769 mg, 4.0 mmol) and Et_3N (729 μL, 5.2 mmol) in dry DCM (50 mL) at 20 °C and the solution stirred for 2 h. The solution was diluted with DCM (50 mL), washed with water (2 × 30 mL), brine (50 mL), the organic fraction dried and the solvent evaporated. The residue was dissolved in THF (50 mL) and morpholine (8.8 mL, 100 mmol) added and the solution heated at reflux temperature for 3 h, then stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between EtOAc (100 mL) and water (100 mL). The aqueous fraction was extracted with EtOAc (3 × 50 mL), the combined organic fraction dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/EtOAc, to give the morpholide **65** (840 mg, 80 %) which was dissolved in HCl saturated MeOH, the solvent evaporated and the residue crystallized as an yellow/orange solid, mp (MeOH/EtOAc) 213-215 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.37 (br s, 1 H, NH^+Cl^-), 8.40 (d, *J* = 8.7 Hz, 1 H, H-8), 8.13 (ddd, *J* = 8.5, 6.9, 1.2 Hz, 1 H, H-6), 8.06 (dd, *J* = 8.5, 1.2 Hz, 1 H, H-5), 7.87 (ddd, *J* = 8.7, 6.9, 1.2 Hz, 1 H, H-7), 3.96-4.01 (m, 2 H, CH_2O), 3.80-3.86 (m, 2 H, CH_2O), 3.63-3.68 (m, 2 H, CH_2N), 3.52-3.58 (m, 4 H, 2 × CH_2N), 3.15-3.25 (m, 2 H, CH_2); Anal. calc. for $C_{13}H_{17}ClN_4O_2$: C, 52.6; H, 5.8; N, 18.9; Cl, 12.0; found C, 52.6; H, 5.5; N, 18.9; Cl, 12.0%.

Example 82

3-(3-Hydroxypropyl)-1,2,4-benzotriazine 1-oxide (66). A solution of 9-BBN in THF (13.7 mL, 6.8 mmol) was added to a stirred solution of alkene **60** (1.07 g, 5.7 mmol) in THF (50 mL) and the solution stirred at 20 °C for 1 h. A solution of NaOH (3 M; 2.9 ml, 8.5 mmol), followed by 35% H_2O_2 (2.6 mL, 25.6 mmol) were carefully added and the mixture stirred at 20 °C for 1 h. The mixture was diluted with brine (100 mL), extracted with EtOAc (3 × 100 mL), the combined organic fraction dried, and the solvent evaporated. The residue was chromatographed, eluting with a gradient (10-50%) of EtOAc/DCM, to give alcohol **66** (1.02 g, 87%) as a white solid, mp (EtOAc/pet. ether) 99-100 °C; ^{1}H NMR δ 8.46 (dd, *J* = 8.7, 1.0 Hz, 1 H, H-8), 7.99 (dd, *J* = 8.5, 1.2 Hz, 1 H, H-5), 7.93 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1 H, H-6), 7.70 (ddd, *J* = 8.7, 7.0, 1.2 Hz, 1 H, H-7), 3.80 (t, *J* = 6.1 Hz, 2 H, CH_2O), 3.18 (t, *J* = 7.3 Hz, 2 H, CH_2), 2.15-2.22 (m, 2 H, CH_2), (OH not observed); ^{13}C NMR δ 166.9, 147.3, 135.7, 133.3, 130.1, 128.6, 120.1, 62.1, 34.1, 30.5; Anal. calc. for $C_{10}H_{11}N_3O_2$: C, 58.5; H, 5.4 ;N, 20.5; found C, 58.6; H, 5.5; N, 20.5%.

Example 83

3-[3-Methoxypropyl]-1,2,4-benzotriazine 1-oxide (67). $TMSCH_2N_2$ (1.1 mL, 2.1 mmol) was added to a stirred solution of alcohol **66** (437 mg, 2.1 mmol) and HBF_4 (0.53 mL, 4.3 mmol) in DCM (20 mL) at 20 °C and the solution stirred for 2 h at 20 °C. More $TMSCH_2N_2$ (5 × 1.1 mL) was added at hourly intervals and the solution stirred vigorously for 16 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (20-35%) of EtOAc/DCM, to give methyl ether **67** (310 mg, 66%) as a tan oil, ^{1}H NMR δ 8.45 (dd, *J* = 8.7, 1.1 Hz, 1 H, H-8), 8.03 (d, *J* = 8.5 Hz, 1 H, H-5), 7.94 (ddd, *J* = 8.5, 7.0, 1.1 Hz, 1 H, H-6), 7.70 (ddd, *J* = 8.7, 7.0, 1.1 Hz, 1 H, H-7), 3.52 (t, *J* = 6.3 Hz, 2 H, CH_2O), 3.33 (s, 3 H, OCH_3), 3.10-3.14 (m, 2 H, CH_2N), 2.16-2.23 (m, 2 H, CH_2); ^{13}C NMR δ 166.8 (C-3), 147.0 (C-4a), 135.7 (C-6), 133.3 (C-8a), 130.0 (C-5), 128.4 (C-7), 120.1 (C-8), 71.7 (CH_2O), 58.5 (OCH_3), 34.0 (CH_2), 32.5 (CH_2); MS (EI) *m/z* 219 (M^+, 25%), 202 (90), 101 (100); HRMS (EI) calc. for $C_{11}H_{13}N_3O_2$ (M^+) *m/z* 219.1008, found 219.1006.

Example 84

***N,N*-Dimethyl-3-(1-oxido-1,2,4-benzotriazin-3-yl)-1-propanamine hydrochloride (68)**. Methanesulfonyl chloride (175 μL, 2.3 mmol) was added to a stirred solution of alcohol **66** (386 mg, 1.9 mmol) and Et_3N (393 μL, 2.8 mmol) in dry DCM (30 mL) at 5 °C and the solution stirred for 2 h at 20 °C. The solution was diluted with DCM (30

mL), washed with water (2 × 20 mL), the organic fraction dried and the solvent evaporated. The residue was dissolved in DMF (5 mL) and 40% aqueous dimethylamine (12 mL, 94 mmol) added and the solution heated at 50 °C for 2 h. The solvent was evaporated and the residue partitioned between EtOAc (50 mL) and water (50 mL). The organic fraction was extracted with water (2 × 25 mL), dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient of (0-1%) Et_3N/(0-5%) MeOH/DCM, to give amine **68** (348 mg, 80%) which was dissolved in HCl saturated MeOH, the solvent evaporated and the residue crystallized as a tan solid, mp (MeOH/EtOAc) 228-230 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.72 (br s, 1 H, NH^+Cl^-), 8.39 (d, *J* = 8.6 Hz, 1 H, H-8), 8.10 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1 H, H-6), 8.06 (dd, *J* = 8.4, 1.5 Hz, 1 H, H-5), 7.86 (ddd, *J* = 8.6, 7.0, 1.5 Hz, 1 H, H-7), 3.04-3.09 (m, 2 H, CH_2N), 3.04 (t, *J* = 7.4 Hz, 2 H, CH_2), 2.74 [s, 6 H, $N(CH_3)_2$], 2.19-2.27 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 164.7 (C-3), 146.8 (C-4a), 136.1 (C-6), 133.0 (C-8a), 130.7 (C-5), 128.4 (C-7), 119.5 (C-8), 55.5 (CH_2N), 41.8 [$N(CH_3)_2$], 33.2 (CH_2), 21.6 (CH_2); Anal. calc. for $C_{12}H_{17}ClN_4O$; C, 53.6; H, 6.4; N, 20.9; found C, 53.9; H, 6.3; N, 21.0%.

Example 85

3-[3-(1-Piperidinyl)propyl]-1,2,4-benzotriazine 1-oxide hydrochloride (69). MsCl (133 μL, 1.7 mmol) was added to a stirred solution of alcohol **66** (293 mg, 1.4 mmol) and Et_3N (300 μL, 2.1 mmol) in dry DCM (20 mL) at 5 °C and the solution stirred for 1 h at 20 °C. The solution was diluted with DCM (30 mL), washed with water (2 × 20 mL), the organic fraction dried and the solvent evaporated. The residue was dissolved in DMF (10 mL) and piperidine (7 mL, 70 mmol) added and the solution heated at 50 °C for 2 h. The solvent was evaporated and the residue partitioned between EtOAc (50 mL) and water (50 mL). The organic fraction was extracted with water (2 × 25 mL), dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-5%) of MeOH/DCM, to give amine **69** (291 mg, 75%) which was dissolved in HCl saturated MeOH, the solvent evaporated and the residue crystallized as a white solid, mp (MeOH/EtOAc) 151-153 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.71 (br s, 1 H, NH^+Cl^-), 8.39 (d, *J* = 8.7 Hz, 1 H, H-8), 8.10 (ddd, *J* = 8.5, 6.9, 1.2 Hz, 1 H, H-6), 8.05 (dd, *J* = 8.5, 1.3 Hz, 1 H, H-5), 7.86 (ddd, *J* = 8.7, 6.9, 1.3 Hz, 1 H, H-7), 3.37-3.43 (m, 2 H, CH_2N), 3.10-3.17 (m, 2 H, CH_2N), 3.03 (t, *J* = 7.4 Hz, 2 H, CH_2), 2.80-2.89 (m, 2 H, CH_2N), 2.25-2.33 (m, 2 H, CH_2), 1.67-1.83 (m, 6 H, 3 × CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 164.8 (C-3), 146.8 (C-4a), 136.1 (C-6), 133.0 (C-8a), 130.7 (C-5), 128.4 (C-7), 119.5 (C-8), 54.8 (CH_2N), 51.8 (2 × CH_2N),

33.42 (CH_2), 22.1 (2 × CH_2), 21.3 (CH_2), 21.0 (CH_2); Anal. calc. for $C_{15}H_{20}N_4O.2HCl$; C, 52.2; H, 6.4; N, 16.3; found C, 52.2; H, 6.4; N, 16.4%.

Example 86

3-[3-(4-Morpholinyl)propyl]-1,2,4-benzotriazine 1-oxide hydrochloride (70). MsCl (137 μL, 1.8 mmol) was added to a stirred solution of alcohol **66** (303 mg, 1.5 mmol) and Et_3N (309 μL, 2.2 mmol) in dry DCM (20 mL) at 5 °C and the solution stirred for 2 h at 20 °C. The solution was diluted with DCM (30 mL), washed with water (2 × 20 mL), the organic fraction dried and the solvent evaporated. The residue was dissolved in DMF (5 mL) and morpholine (6.4 mL, 74 mmol) added and the solution heated at 50 °C for 2 h. The solvent was evaporated and the residue partitioned between EtOAc (50 mL) and water (50 mL). The organic fraction was extracted with water (2 × 25 mL), dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-5%) of MeOH/30% EtOAc/DCM, to give the morpholide **70** (330 mg, 81%) which was dissolved in HCl saturated MeOH, the solvent evaporated and the residue crystallized as a tan solid, mp (MeOH) 175-177 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.54 (br s, 1 H, NH^+Cl^-), 8.39 (dd, *J* = 8.7, 1.0 Hz, 1 H, H-8), 8.10 (ddd, *J* = 8.4, 6.9, 1.0 Hz, 1 H, H-6), 8.06 (dd, *J* = 8.4, 1.0 Hz, 1 H, H-5), 7.86 (ddd, *J* = 8.7, 6.9, 1.0 Hz, 1 H, H-7), 3.82-3.96 (m, 4 H, 2 × CH_2O), 3.38-3.43 (m, 2 H, CH_2), 3.18-3.23 (m, 2 H, CH_2N), 2.98-3.08 (m, 4 H, 2 × CH_2N), 2.26-2.33 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 164.7 (C-3), 146.8 (C-4a), 136.2 (C-6), 133.0 (C-8a), 130.7 (C-5), 128.4 (C-7), 119.5 (C-8), 63.0 (2 × CH_2O), 55.0 (CH_2N), 50.8 (2 × CH_2N), 33.4 (CH_2), 20.7 (CH_2).

Example 87

3-Methoxy-1,2,4-benzotriazine 1-oxide (71). A solution of NaOMe [prepared from the dissolution of Na (57 mg, 2.5 mmol) in dry MeOH (10 mL)] and chloride **19** (298 mg, 1.6 mmol) was stirred at 20 °C for 3 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and water (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with 5% EtOAc/DCM, to give 1-oxide **71** (257 mg, 88%) as pale yellow needles, mp (EtOAc/pet. ether) 123-124 °C [lit (Ergener, Istanbul Univ. Fen. Fak. Mecm. Seri. A, **1950**, *15*, 91) mp (MeOH) 121-122 °C]; ^{1}H NMR δ 8.38 (dd, *J* = 8.4, 0.7 Hz, 1 H, H-8), 7.83-7.88 (m, 2 H, H-5, H-6), 7.54 (ddd, *J* = 8.4, 6.2, 2.2 Hz, 1 H, H-7), 4.16 (s, 3 H, OCH_3); ^{13}C NMR δ 162.6 (C-3), 147.4 (C-4a), 135.9 (C-6), 132.4 (C-8a), 127.6 (C-5), 127.5 (C-7), 120.5 (C-8), 55.6 (OCH_3).

Example 88

3-(2-Methoxyethoxy)-1,2,4-benzotriazine 1-oxid (72). Na (123 mg, 5.3 mmol) was added to a solution of chloride **19** (645 mg, 3.6 mmol) in 2-methoxyethanol (20 mL) at 5 °C. The mixture was stirred at 20 °C for 2 h, diluted with water (80 mL), extracted with EtOAc (3 × 80 mL), the organic fraction dried , and the solvent evaporated. The residue was chromatographed, eluting with 10%EtOAc/DCM, to give 1-oxide **72** (618 mg, 79%) as white needles, mp (EtOAc/pet. ether) 74-76 °C; ^{1}H NMR δ 8.37 (dd, *J* = 8.7, 1.3 Hz, 1 H, H-8), 7.81-7.88 (m, 2 H, H-5, H-6), 7.53 (ddd, *J* = 8.7, 6.7, 1.8 Hz, 1 H, H-7), 4.65-4.68 (m, 2 H, CH_2O), 3.81-3.84 (m, 2 H, CH_2O), 3.46 (s, 3 H, OCH_3); ^{13}C NMR δ 162.1 (C-3), 147.4 (C-4a), 135.9 (C-6), 132.5 (C-8a), 127.6 (C-5), 127.5 (C-7), 120.4 (C-8), 70.2 (CH_2O), 67.6 (CH_2O), 59.2 (OCH_3); Anal. calc. for $C_{10}H_{11}N_3O_3$: C, 54.3; H, 5.0; N, 19.0; found C, 54.4; H, 4.9; N, 19.0%.

Example 89

3-Chloro-6-methyl-1,2,4-benzotriazine 1-oxide (73). Sodium nitrite (7.09 g, 103 mmol) was added in small portions to a stirred solution of 6-methyl-1,2,4-benzotriazin-3-amine 1-oxide (**3r**) (9.05 g, 51.4 mmol) in trifluoroacetic acid (80 mL) at 5 °C and the solution stirred at 20 °C for 3 h. The solution was poured into ice/water, stirred 30 minutes, filtered, washed with water (3 × 30 mL) and dried. The solid was suspended in $POCl_3$ (100 mL) and DMF (0.5 mL) and stirred at 100 °C for 1 h. The solution was cooled, poured into ice/water, stirred for 30 minutes, filtered, washed with water (3 × 30 mL) and dried. The solid was suspended in DCM (150 mL), dried and the solvent evaporated. The residue was chromatographed, eluting with 5% EtOAc/DCM, to give chloride **73** (7.86 g, 78%) as a pale yellow solid, mp (EtOAc/DCM) 156-158 °C; ^{1}H NMR δ 8.29 (d, *J* = 8.8 Hz, 1 H, H-8), 7.74 (d, *J* = 1.7 Hz, 1 H, H-5), 7.56 (dd, *J* = 8.8, 1.7 Hz, 1 H, H-7), 2.61 (s, 3 H, CH_3); Anal. calc. for $C_8H_6ClN_3O$: C, 49.1; H, 3.1; N, 21.5; found C, 49.2; H, 3.4; N, 21.5%.

Example 90

2-[(6-Methyl-1-oxido-1,2,4-benzotriazin-3-yl)amino]ethanol (74). 2-Aminoethanol (0.61 mL, 10.1 mmol) was added to a stirred solution of chloride **73** (657 mg, 3.4 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 16 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and dilute aqueous NH_3 (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (5-10%) of

MeOH/DCM, to give 1-oxide **74** (700 mg, 95%) as a yellow powder, mp (MeOH) 198-202 °C; ^{1}H NMR δ 8.00 (d, *J* = 8.8 Hz, 1 H, H-8), 7.70 (br s, 1 H, NH), 7.35 (d, *J* = 1.7 Hz, 1 H, H-5), 7.15 (dd, *J* = 8.8, 1.7 Hz, 1 H, H-7), 4.70 (t, *J* = 5.6 Hz, 1 H, OH), 3.54-3.60 (m, 2 H, CH_2O), 3.38-3.43 (m, 2 H, CH_2N), 2.47 (s, 3 H, CH_3); ^{13}C NMR δ 159.1 (C-3), 148.4 (C-4a), 146.6 (C-6), 128.2 (C-8a), 126.4 (C-5), 125.7 (C-7), 119.5 (C-8), 59.2 (CH_2O), 43.2 (CH_2N), 21.3 (CH_3); Anal. calc. for $C_{10}H_{12}N_4O_2$: C, 54.5; H, 5.5; N, 25.4; found C, 54.7; H, 5.4; N, 25.7%.

Example 91

***N*-(2-Methoxyethyl)-6-methyl-1,2,4-benzotriazin-3-amine 1-oxide (75).** 2-Methoxyethylamine (0.44 mL, 5.0 mmol) was added to a stirred solution of chloride **73** (329 mg, 1.7 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 2 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and dilute aqueous NH_3 (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (5-40%) of EtOAc/DCM, to give 1-oxide **75** (368 mg, 93%) as a yellow powder, mp (MeOH) 157-158 °C; ^{1}H NMR δ 8.14 (d, *J* = 8.8 Hz, 1 H, H-8), 7.36 (d, *J* = 1.7 Hz, 1 H, H-5), 7.10 (dd, *J* = 8.8, 1.7 Hz, 1 H, H-7), 5.58 (br s, 1 H, NH), 3.68-3.72 (m, 2 H, CH_2N), 3.59-3.62 (m, 2 H, CH_2O), 3.39 (s, 3 H, OCH_3), 2.47 (s, 3 H, CH_3); ^{13}C NMR δ 159.1 (C-3), 149.1 (C-4a), 147.0 (C-6), 129.3 (C-8a), 127.2 (C-5), 125.4 (C-7), 120.1 (C-8), 70.9 (CH_2O), 58.8 (OCH_3), 41.1 (CH_2N), 22.0 (CH_3); Anal. calc. for $C_{11}H_{14}N_4O_2$: C, 56.4; H, 6.0; N, 23.9; found C, 56.4; H, 5.9; N, 23.8%.

Example 92

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(6-methyl-1-oxido-1,2,4-benzotriazin-3-yl)-1,2-ethanediamine (76).** *N*,*N*-Dimethylethanediamine (705 μL, 6.6 mmol) was added to a stirred solution of chloride **73** (518 mg, 2.7 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 2 h. The solution was cooled, the solvent evaporated and the residue partitioned between dilute aqueous NH_3 (100 mL) and DCM (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **76** (603 mg, 92%) as a yellow solid, mp (MeOH/EtOAc) 143-145 °C; ^{1}H NMR δ 8.11 (d, *J* = 8.8 Hz, 1 H, H-8), 7.35 (d, *J* = 1.7 Hz, 1 H, H-5), 7.07 (dd, *J* = 8.8, 1.7 Hz, 1 H, H-7), 5.89 (br s, 1 H, NH), 3.50-3.56 (m, 2 H, CH_2N), 2.52-2.56 (m, 2 H, CH_2N), 2.45 (s, 3 H, CH_3), 2.26 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR δ 159.2 (C-3), 149.1 (C-4a), 146.9 (C-6), 129.2 (C-8a), 126.9 (C-5), 125.3 (C-7), 120.1 (C-8), 57.5 (CH_2N), 45.1 [$N(CH_3)_2$], 38.7 (CH_2N), 22.0

(CH_3); Anal. calc. for $C_{12}H_{17}N_5O$: C, 58.3; H, 6.9; N, 28.3; found C, 58.5: H, 7.1; N, 28.6%.

Example 93

6-Methyl-*N*-[2-(1-piperidinyl)ethyl]-1,2,4-benzotriazin-3-amine 1-oxide (77). 2-(1-Piperidinyl)ethylamine (0.87 mL, 6.1 mmol) was added to a stirred solution of chloride **73** (476 mg, 2.4 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 2 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and dilute aqueous NH_3 (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **77** (656 mg, 94%) as a yellow powder, mp (MeOH/EtOAc) 156-158 °C; ^{1}H NMR δ 8.13 (d, J = 8.7 Hz, 1 H, H-8), 7.36 (d, J = 1.7 Hz, 1 H, H-5), 7.08 (dd, J = 8.7, 1.7 Hz, 1 H, H-7), 5.98 (br s, 1 H, NH), 3.51-3.56 (m, 2 H, CH_2N), 2.54-2.58 (m, 2 H, CH_2N), 2.47 (s, 3 H, CH_3), 2.39-2.45 (m, 4 H, 2 × CH_2N), 1.55-1.61 (m, 4 H, 2 × CH_2), 1.42-1.48 (m, 2 H, CH_2); ^{13}C NMR δ 159.1 (C-3), 149.1 (C-4a), 146.9 (C-6), 129.1 (C-8a), 126.9 (C-7), 125.3 (C-5), 120.1 (C-8), 56.9 (CH_2N), 54.3 (2 × CH_2N), 37.9 (CH_2N), 26.0 (2 × CH_2), 24.4 (CH_2), 22.0 (CH_3); Anal. calc. for $C_{15}H_{21}N_5O$: C, 62.7; H, 7.4; N, 24.4; found C, 62.8; H, 7.7; N, 24.5%.

Example 94

***N*-[2-(2,6-Dimethyl-1-piperidinyl)ethyl]- 6-methyl-1,2,4-benzotriazin-3-amine 1-oxide (78).** 2-(2,6-Dimethyl-1-piperidinyl)ethylamine (834 mg, 5.3 mmol) was added to a stirred solution of chloride **73** (418 mg, 2.1 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 2 h. The solution was cooled, the solvent evaporated and the residue partitioned between dilute aqueous NH_3 (100 mL) and DCM (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **78** (597 mg, 93%) as a yellow solid, mp (MeOH/EtOAc) 162-165 °C; ^{1}H NMR δ 8.12 (d, J = 8.9 Hz, 1 H, H-8), 7.35 (d, J = 1.7 Hz, 1 H, H-5), 7.09 (dd, J = 8.9, 1.7 Hz, 1 H, H-7), 5.57 (br s, 1 H, NH), 3.50-3.56 (m, 2 H, CH_2N), 2.87-2.91 (m, 2 H, CH_2N), 2.49-2.57 (m, 2 H, 2 × CH), 2.47 (s, 3 H, CH_3), 1.65-1.69 (m, 1 H, CH_2), 1.53-1.58 (m, 2 H, CH_2), 1.25-1.41 (m, 3 H, CH_2), 1.19 (d, J = 6.3 Hz, 6 H, 2 × CH_3); ^{13}C NMR δ 159.2 (C-3), 149.1 (C-4a), 146.9 (C-6), 129.2 (C-8a), 127.0 (C-5), 125.4 (C-7), 120.8 (C-8), 57.3 (2 × CH), 47.4 (CH_2N), 39.5 (CH_2N), 34.2 (CH_2), 24.4 (2 × CH_2), 22.0 (2 × CH_3), 21.6 (CH_3); Anal. calc. for $C_{17}H_{25}N_5O$: C, 64.7; H, 8.0; N, 22.2; found C, 64.3: H, 7.3; N, 22.0%.

Example 95

3-Ethyl-6-m thyl-1,2,4-benzotriazin 1-oxide (79). $Pd(PPh_3)_4$ (410 mg, 0.35 mmol) was added to a stirred solution of chloride **73** (728 mg, 3.6 mmol) and tetraethyltin (1.4 mL, 7.1 mmol), the solution degassed, and stirred under N_2 at reflux temperature for 16 h. The solvent was evaporated and the residue chromatographed, eluting with 20% EtOAc/pet. ether to give an oil which was chromatographed, eluting with 5% EtOAc/DCM, to give (i) starting material **73** (412 mg, 56%) and (ii) 1-oxide **79** (250 mg, 37%) as a white solid, mp (EtOAc/DCM) 68-70 °C; ^{1}H NMR δ 8.33 (d, J = 8.8 Hz, 1 H, H-8), 7.74 (br s, 1 H, H-5), 7.49 (dd, J = 8.8, 1.7 Hz, 1 H, H-7), 3.02 (q, J = 7.6 Hz, 2 H, CH_2), 2.59 (s, 3 H, CH_3), 1.44 (t, J = 7.6 Hz, 3 H, CH_3); ^{13}C NMR δ 168.2 (C-3), 147.8 (C-4a), 147.1 (C-6), 132.0 (C-5), 131.6 (C-8a), 127.5 (C-7), 119.8 (C-8), 30.7 (CH_2), 22.1 (CH_3), 12.2 (CH_3); Anal. calc. for $C_{10}H_{11}N_3O$: C, 63.5; H, 5.9; N, 22.2; found C, 63.5; H, 6.0; N, 22.3%.

Example 96

3-Allyl-6-methyl-1,2,4-benzotriazine 1-oxide (80). $Pd(PPh_3)_4$ (370 mg, 0.32 mmol) was added to a stirred solution of chloride **73** (1.24 g, 6.3 mmol) and allyltributyltin (2.2 mL, 7.0 mmol), the solution degassed, and stirred under N_2 at reflux temperature for 6 h. The solvent was evaporated and the residue chromatographed, eluting with 20% EtOAc/pet. ether, to give an oil which was chromatographed, eluting with 5% EtOAc/DCM, to give alkene **80** (0.97 g, 74%) as a white solid, mp (EtOAc/pet. ether) 65-67 °C, ^{1}H NMR δ 8.32 (d, J = 8.8 Hz, 1 H, H-8), 7.76 (d, J = 1.7 Hz, 1 H, H-5), 7.50 (dd, J = 8.8, 1.7 Hz, 1 H, H-7), 6.13-6.21 (m, 1 H, H-2'), 5.30 (dq, J = 17.0, 1.5 Hz, 1 H, H-3'), 5.22 (dq, J = 10.1, 1.5 Hz, 1 H, H-3'), 3.76 (dq, J = 6.9, 1.5 Hz, 2 H, H-1'), 2.58 (s, 3 H, CH_3); ^{13}C NMR δ 165.3 (C-3), 147.8 (C-4a), 147.3 (C-6), 132.8 (C-2'), 132.5 (C-5), 131.6 (C-8a), 127.6 (C-7), 119.7 (C-8), 118.4 (C-3'), 41.8 (C-1'), 22.1 (CH_3); Anal. calc. for $C_{11}H_{11}N_3O$: C, 65.7; H, 5.5; N, 20.9; found C, 65.8; H, 5.5; N, 21.0%.

Example 97

2-(6-Methyl-1-oxido-1,2,4-benzotriazin-3-yl)ethanol (81). Ozone was bubbled into a solution of alkene **80** (1.12 g, 5.6 mmol) in DCM/MeOH (1:1, 80 mL) at -78 °C until a blue colour persisted. The solution was purged with N_2 to remove excess ozone, then a solution of $NaBH_4$ (210 mg, 5.6 mmol) in EtOH (10 mL) added dropwise and the solution allowed to warm to 20 °C over 1 h. HOAc (2 mL) was added and the

solution stirred at 20 °C for 30 min. The solvent was evaporated and the residue partitioned between DCM (50 mL) and water (3 × 50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (50-100%) of EtOAc/pet. ether, to give alcohol **81** (780 mg, 68%) as pale yellow prisms, mp (EtOAc/pet. ether) 121-123 °C; ^{1}H NMR δ 8.32 (d, *J* = 8.8 Hz, 1 H, H-8), 7.74 (d, J = 1.7 Hz, 1 H, H-5), 7.50 (dd, *J* = 8.8, 1.7 Hz, 1 H, H-7), 4.04-4.10 (m, 2 H, CH_2O), 3.27 (t, *J* = 5.6 Hz, 2 H, CH_2), 3.17 (t, *J* = 6.3 Hz, 1 H, OH), 2.60 (s, 3 H, CH_3); ^{13}C NMR δ 165.5 (C-3), 147.6 (C-4a), 147.3 (C-6), 132.4 (C-5), 131.9 (C-8a), 127.4 (C-7), 119.8 (C-8), 60.1 (CH_2O), 39.0 (CH_2), 22.1 (CH_3); Anal. calc for $C_{10}H_{11}N_3O_2$: C, 58.5; H, 5.4; N, 20.5; found C, 58.8; H, 5.5; N, 20.5%.

Example 98

3-(2-Methoxyethyl)-6-methyl-1,2,4-benzotriazine 1-oxide (82). Three aliquots of $TMSCH_2N_2$ (1.1 mL, 2.1 mmol) were added to a stirred solution of alcohol **81** (433 mg, 2.1 mmol) and HBF_4 (0.26 mL, 2.1 mmol) in DCM (30 mL) over 3 h. The solution was stirred at 20 °C for 16 h, the solvent evaporated and the residue chromatographed, eluting with 50% EtOAc/pet. ether, to give (i) methyl ether **82** (119 mg, 19%) as a yellow powder, mp (EtOAC/pet. ether) 77-79 °C; ^{1}H NMR δ 8.32 (d, *J* = 8.8 Hz, 1 H, H-8), 7.56 (d, *J* = 1.7 Hz, 1 H, H-5), 7.50 (dd, *J* = 8.8, 1.7 Hz, 1 H, H-6), 3.95 (t, *J* = 6.5 Hz, 2 H, CH_2O), 3.37 (s, 3 H, OCH_3), 3.27 (t, *J* = 6.5 Hz, 2 H, CH_2), 2.58 (s, 3 H, CH_3); ^{13}C NMR δ 164.7 (C-3), 147.7 (C-4a), 147.2 (C-6), 132.2 (C-5), 131.8 (C-8a), 127.6 (C-7), 119.7 (C-8), 70.1 (CH_2O), 58.7 (OCH_3), 37.6 (CH_2), 22.1 (CH_3); and (ii) starting material **81** (360 mg, 62%), spectroscopically identical to sample prepared above.

Example 99

3-Chloro-6-methoxy-1,2,4-benzotriazine 1-oxide (83). Sodium nitrite (7.14 g, 103.4 mmol) was added in portions to a stirred solution of 6-methoxy-1,2,4-benzotriazin-3-amine 1-oxide **3q** (9.94 g, 51.7 mmol) in trifluoroacetic acid (50 mL) at 5 °C and the solution stirred at 20 °C for 1 h. The solution was poured into ice/water, filtered, washed with water (2 × 50 mL) and dried. The solid was suspended in $POCl_3$ (80 mL), DMF (2 drops) added, and the mixture stirred at 100 °C for 3 h. The solution was poured into ice/water, stirred for 20 minutes and filtered. The solid was dissolved in DCM (150 mL), dried, and the solvent evaporated. The residue was chromatographed, eluting with 5% EtOAc/DCM, to give chloride **83** (7.42 g, 68%) as a pale yellow solid, mp (EtOAc/DCM) 196-199 °C; ^{1}H NMR δ 8.30 (d, *J* = 9.6 Hz, 1 H,

H-8), 7.32 (dd, J = 9.6, 2.7 Hz, 1 H, H-7), 7.19 (d, J = 2.7 Hz, 1 H, H-5), 4.01 (s, 3 H, OCH_3); ^{13}C NMR δ 166.3 (C-6), 157.8 (C-3), 150.2 (C-4a), 128.9 (C-8a), 123.9 (C-5), 121.9 (C-7), 105.7 (C-8), 56.5 (OCH_3); Anal. calc. for $C_8H_8ClN_3O_2$: C, 45.4; H, 2.9; N, 19.9; Cl, 16.8; found C, 45.2; H, 2.6; N, 19.9; Cl, 16.9%.

Example 100

***N*^{1}-(6-Methoxy-1-oxido-1,2,4-benzotriazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (84).** *N*,*N*-Dimethyl-1,2-ethanediamine (1.33 mL, 12.1 mmol) was added to a stirred solution of chloride **83** (0.85 g, 4.04 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 16 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and dilute aqueous NH_3 (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-5%) of MeOH/DCM, to give amine **84** (0.72 g, 68%) which was dissolved in HCl saturated MeOH, the solvent evaporated and the residue crystallized as a tan solid, mp (MeOH/EtOAc) 236-239 °C; ^1H NMR [$(CD_3)_2SO$] δ 10.68 (br s, 1 H, NH^+Cl^-), 8.07 (d, J = 9.3 Hz, 1 H, H-8), 8.03 (br s, 1 H, NH), 6.95-6.99 (m, 2 H, H-5, H-7), 3.92 (s, 3 H, OCH_3), 3.70-3.76 (m, 2 H, CH_2N), 3.30-3.35 (m, 2 H, CH_2N), 2.81 [d, J = 4.9 Hz, 6 H, $N(CH_3)_2$]; ^{13}C NMR [$(CD_3)_2SO$] δ 164.9 (C-6), 159.0 (C-3), 150.4 (C-4a), 125.4 (C-8a), 121.6 (C-8), 117.3 (C-5), 104.3 (C-7), 55.2 (OCH_3), 55.2 (CH_2N), 42.3 [$N(CH_3)_2$], 35.8 (CH_2N); Anal. calc. for $C_{12}H_{18}ClN_5O_2$: C, 48.1; H, 6.1; N, 23.4; Cl, 11.8; found C, 48.3; H, 6.1; N, 23.6; Cl, 11.9%.

Example 101

6-Methoxy-*N*-[2-(1-piperidinyl)ethyl]-1,2,4-benzotriazin-3-amine 1-oxide (85). 2-(1-Piperidinyl)ethylamine (0.9 mL, 6.0 mmol) was added to a stirred solution of chloride **83** (509 mg, 2.4 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 2 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and dilute aqueous NH_3 (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **85** (736 mg, 100%) as a yellow powder, mp (MeOH) 133-135 °C; ^1H NMR δ 8.15 (d, J = 9.8 Hz, 1 H, H-8), 6.85-6.88 (m, 2 H, H-5, H-7), 6.00 (br s, 1 H, NH), 3.92 (s, 3 H, OCH_3), 3.52-3.56 (m, 2 H, CH_2N), 2.56-2.60 (m, 2 H, CH_2N), 2.38-2.44 (m, 4 H, 2 × CH_2N), 1.56-1.62 (m, 4 H, 2 × CH_2), 1.42-1.48 (m, 2 H, CH_2); ^{13}C NMR δ 165.4 (C-7), 159.5 (C-3), 151.5 (C-4a), 126.0 (C-8a), 122.0 (C-7), 117.6 (C-8), 104.5 (C-5), 56.8 (CH_2N), 56.0 (OCH_3), 54.3 (2 × CH_2N),

37.9 (CH_2N), 26.0 (2 × CH_2), 24.4 (CH_2); Anal. calc. for $C_{15}H_{21}N_5O_2.H_2O$: C, 56.1; H, 7.2; N, 21.8; found C, 55.9; H, 7.0; N, 21.7%.

Example 102

6-Methoxy-*N*-[2-(4-morpholinyl)ethyl]-1,2,4-benzotriazin-3-amine 1-oxide (86). 2-(4-Morpholinyl)ethylamine (1.92 mL, 14.6 mmol) was added to a stirred solution of chloride **83** (1.03 g, 4.9 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 16 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and dilute aqueous NH_3 (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-5%) of MeOH/DCM, to give amine **86** (0.89 g, 60%) as a yellow powder, mp (MeOH/EtOAc) 186-188 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.03 (d, J = 9.5 Hz, 1 H, H-8), 7.63 (br s, 1 H, NH), 6.90-6.95 (m, 2 H, H-5, H-7), 3.91 (s, 3 H, OCH_3), 3.55-3.58 (m, 4 H, 2 × CH_2O), 3.45-3.49 (m, 2 H, CH_2N), 2.50-2.55 (m, 2 H, CH_2N), 2.41-2.44 (m, 4 H, 2 × CH_2N); ^{13}C NMR [$(CD_3)_2SO$] δ 164.8 (C-6), 159.4 (C-3), 150.9 (C-4a), 125.0 (C-8a), 121.5 (C-8), 116.8 (C-7), 104.2 (C-5), 66.1 (2 × CH_2O), 56.8 (CH_2N), 56.1 (OCH_3), 53.2 (2 × CH_2N), 37.7 (CH_2N); Anal. calc. for $C_{14}H_{19}N_5O_3.¼H_2O$: C, 54.3; H, 6.3; N, 22.6; found C, 54.5; H, 6.2; N, 22.8%.

Example 103

3-Chloro-7-methyl-1,2,4-benzotriazine 1-oxide (87). A solution of $NaNO_2$ (3.9 g, 56.3 mmol) in water (15 mL) was added dropwise to a stirred suspension of amine **3j** (4.95 g, 28.1 mmol) in 2 M HCl (200 mL) at 5 °C and the mixture stirred vigorously for 2 h at 20 °C. The suspension was filtered, the solid dissolved in dilute aqueous NH_3 (150 mL), filtered and the filtrate acidified with cHCl. The suspension was cooled, filtered and the solid washed with water (2 × 10 mL) and dried. The solid (3.76 g, 21.2 mmol) was suspended in dimethylaniline (6.7 mL, 53 mmol) and $POCl_3$ (14 mL, 149 mmol). The mixture was stirred at relux temperature for 1 h, the resulting solution poured on to ice (300 mL). The suspension was filtered, washed with water (2 × 20 mL), dissolved in EtOAc (200 mL), dried and the solvent evaporated. The residue was chromatographed, eluting with 5% EtOAc/DCM, to give chloride **87** (2.99 g, 72 %) as a yellow solid, mp 176.5-177 °C [lit (Foye et. al., *J. Het. Chem.* **1982**, *19*, 497) mp (toluene) 177-179 °C]; ^{1}H NMR δ 8.21 (d, J = 2.0 Hz, 1 H, H-8), 7.89 (d, J = 8.6 Hz, 1 H, H-5), 7.81 (dd, J = 8.6, 2.0 Hz, 1 H, H-6), 2.61 (s, 3 H, CH_3).

Example 104

7-Methyl-*N*-[2-(dim thylamino)ethyl]-1,2,4-benzotriazin-3-amine 1-oxide (88). 2-(Dimethylamino)ethylamine (1.0 mL, 9.0 mmol) was added to a stirred solution of chloride **87** (700 mg, 3.6 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 8 h. The solution was cooled, the solvent evaporated and the residue partitioned between dilute aqueous NH_3 (100 mL) and DCM (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) MeOH/DCM, to give 1-oxide **88** (781 mg, 88%) as a yellow solid, mp (DCM) 143-144 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.93 (br s, 1 H, H-8), 7.60-7.64 (m, 2 H, NH, H-6), 7.48 (d, J = 8.6 Hz, 1 H, H-5), 3.37-3.45 (m, 2 H, CH_2N), 2.46-2.52 (m, 2 H, CH_2N), 2.41 (s, 3 H, CH_3), 2.21 [m, 6 H, $N(CH_3)_2$]; ^{13}C NMR [$(CD_3)_2SO$] δ 158.6 (C-3), 146.8 (C-4a), 137.6 (C-6), 134.6 (C-7), 129.6 (C-8a), 125.8 (C-5), 118.4 (C-8), 57.6 (CH_2N), 45.1 [$N(CH_3)_2$], 39.0 (CH_2N), 20.6 (CH_3); Anal. calc. for $C_{12}H_{17}N_5O$: C, 58.3; H, 6.9; N, 28.3; found C, 58.5: H, 7.2; N, 28.6%

Example 105

7-Methyl-*N*-[2-(1-piperidinyl)ethyl]-1,2,4-benzotriazin-3-amine 1-oxide (89). 2-(1-Piperidinyl)ethylamine (0.83 mL, 5.8 mmol) was added to a stirred solution of chloride **87** (453 mg, 2.3 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 2 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and dilute aqueous NH_3 (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **89** (635 mg, 95%) as a yellow powder, mp (MeOH) 166-168 °C; ^{1}H NMR δ 8.04-8.06 (m, 1 H, H-8), 7.52 (dd, J = 8.7, 1.8 Hz,1 H, H-6), 7.49 (d, J = 8.7 Hz, 1 H, H-5), 5.95 (br s, 1 H, NH), 3.52-3.56 (m, 2 H, CH_2N), 2.56-2.59 (m, 2 H, CH_2N), 2.45 (s, 3 H, CH_3), 2.40-2.44 (m, 4 H, 2 × CH_2N), 1.55-1.61 (m, 4 H, 2 × CH_2), 1.42-1.47 (m, 2 H, CH_2); ^{13}C NMR δ 158.7 (C-3), 147.7 (C-4a), 137.6 (C-6), 135.3 (C-7), 130.4 (C-8a), 126.1 (C-5), 119.2 (C-8), 56.9 (CH_2N), 54.3 (2 × CH_2N), 37.9 (CH_2N), 26.0 (2 × CH_2), 24.4 (CH_2), 21.3 (CH_3); Anal. calc. for $C_{15}H_{21}N_5O$: C, 62.7; H, 7.4; N, 24.4; found C, 62.8; H, 7.1; N, 24.7%.

Example 106

7-Methyl-*N*-[3-(4-morpholinyl)propyl]-1,2,4-benzotriazin-3-amin 1-oxide (90). 3-(4-Morpholinyl)propylamine (1.4 mL, 9.4 mmol) was added to a stirred solution of chloride **87** (738 mg, 3.8 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 8 h. The solution was cooled, the solvent evaporated and the residue

partitioned between dilute aqueous NH_3 (100 mL) and DCM (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **90** (1.12 g, 98%) as a yellow powder, mp 158-160 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.94 (d, J = 1.7 Hz, 1 H, H-8), 7.80 (br s, 1 H, NH), 7.63 (dd, J = 8.6, 1.7 Hz, 1 H, H-6), 7.47 (d, J = 8.6 Hz, 1 H, H-5), 3.53-3.57 (m, 4 H, 2 × CH_2O), 3.36-3.39 (m, 2 H, CH_2N), 2.41 (s, 3 H, CH_3), 2.31-2.38 (m, 6 H, 3 × CH_2N), 1.71-1.77 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 158.6 (C-3), 146.8 (C-4a), 137.6 (C-6), 134.5 (C-7), 129.6 (C-8a), 125.7 (C-5), 118.4 (C-8), 66.1 (2 × CH_2O), 55.8 (CH_2N), 53.2 (2 × CH_2N), 38.9 (CH_2N), 25.3 (CH_2), 20.6 (CH_3); Anal. calc. for $C_{15}H_{21}H_5O_2$: C, 59.4; H, 7.0; N, 23.1; found C, 59.7: H, 7.2; N, 23.2%

Example 107

3-Chloro-7-methoxy-1,2,4-benzotriazine 1-oxide (91). A solution of $NaNO_2$ (6.45 g, 93.6 mmol) in water (25 mL) was added dropwise to a stirred suspension of amine **3i** (9.0 g, 46.8 mmol) in 2 M HCl (500 mL) at 5 °C and the foaming suspension stirred vigourously for 2 h. The solid was filtered, dissolved in dilute aqueous NH_3, filtered, the filtrate acidified with conc. HCl, and cooled. The resulting precipitate was filtered, washed with water and dried. The solid was dissolved in $POCl_3$ (100 mL) and DMF (0.5 mL) and heated at 100 °C for 1 h. The solution was cooled, poured into ice/water, stirred for 30 minutes, filtered, washed with water (3 × 30 mL) and dried. The solid was suspended in DCM (150 mL), dried and the solvent evaporated. The residue was chromatographed, eluting with 5% EtOAc/DCM, to give chloride **87** (7.10 g, 71%) as a pale yellow solid, mp (EtOAc/DCM) 177-179 °C [lit (Sasse et. al, *Ger. Offen.* 2,740,887, 1979) mp (benzene) 164-165 °C]; ^{1}H NMR δ 7.91 (d, J = 9.2 Hz, 1 H, H-5), 7.69 (d, J = 2.9 Hz, 1 H, H-8), 7.64 (dd, J = 9.2, 2.9 Hz, 1 H, H-6), 4.03 (s, 3 H, OCH_3); ^{13}C NMR δ 161.7 (C-7), 154.7 (C-3), 143.6 (C-4a), 130.0 (C-8, C-8a), 129.6 (C-6), 97.8 (C-5), 56.6 (OCH_3).

Example 108

***N*^{1}-(7-Methoxy-1-oxido-1,2,4-benzotriazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (92).** *N*,*N*-dimethylethylenediamine (1.0 mL, 9.3 mmol) was added to a stirred solution of chloride **91** (659 mg, 3.1 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 16 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and dilute aqueous NH_3 (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give the amine **92** (820 mg, 90%)

as a yellow powder, which was recrystallized as the hydrochloride salt, mp (MeOH/EtOAc) 231-235 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.61 (br s, 1 H, NH^+Cl^-), 7.89 (br s, 1 H, NH), 7.59 (d, J = 8.9 Hz, 1 H, H-5), 7.49-7.53 (m, 2 H, H-6, H-8), 3.88 (s, 3 H, OCH_3), 3.69-3.73 (m, 2 H, CH_2N), 3.28-3.32 (m, 2 H, CH_2N), 2.82 [d, J = 4.9 Hz, 6 H, $N(CH_3)_2$]; ^{13}C NMR [$(CD_3)_2SO$] δ 157.8 (C-7), 156.7 (C-3), 144.0 (C-4a), 130.3 (C-8a), 128.3 (C-5), 127.6 (C-6), 98.1 (C-8), 55.9 (OCH_3), 55.3 (CH_2N), 42.3 [$N(CH_3)_2$], 35.8 (CH_2N); Anal. calc. for $C_{12}H_{18}ClN_5O_2$: C, 48.1; H, 6.1; N, 23.4; Cl, 11.8; found C, 48.1; H, 6.2; N, 23.5; Cl, 12.0%.

Example 109

7-Methoxy-*N*-[2-(1-piperidinyl)ethyl]-1,2,4-benzotriazin-3-amine 1-oxide (93). 2-(1-Piperidinyl)ethylamine (0.8 mL, 5.4 mmol) was added to a stirred solution of chloride **91** (453 mg, 2.1 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 16 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and dilute aqueous NH_3 (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **93** (625 mg, 96%) as a yellow powder, mp (MeOH) 162-165 °C; ^{1}H NMR δ 7.58 (d, J = 2.8 Hz, 1 H, H-8), 7.53 (d, J = 9.2 Hz, 1 H, H-5), 7.38 (dd, J = 9.2, 2.8 Hz, 1 H, H-6), 5.90 (br s, 1 H, NH), 3.91 (s, 3 H, OCH_3), 3.52-3.56 (m, 2 H, CH_2N), 2.56-2.60 (m, 2 H, CH_2N), 2.46-2.56 (m, 4 H, 2 × CH_2N), 1.56-1.62 (m, 4 H, 2 × CH_2), 1.43-1.48 (m, 2 H, CH_2); ^{13}C NMR δ 158.4 (C-7), 157.2 (C-3), 145.3 (C-4a), 130.7 (C-8a), 128.8 (C-5), 127.7 (C-6), 98.2 (C-8), 56.9 (CH_2N), 56.0 (OCH_3), 54.3 (2 × CH_2N), 38.2 (CH_2N), 26.0 (2 × CH_2), 24.4 (CH_2); Anal. calc. for $C_{15}H_{21}N_5O_2$: C, 59.4; H, 7.0; N, 23.1; found C, 59.1; H, 6.7; N, 23.2%.

Example 110

7-Methoxy-*N*-[2-(4-morpholinyl)ethyl]-1,2,4-benzotriazin-3-amine 1-oxide (94). 2-(4-Morpholinyl)ethylamine (1.2 mL, 9.0 mmol) was added to a stirred solution of chloride **91** (633 mg, 3.0 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 16 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and dilute aqueous NH_3 (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-5%) of MeOH/DCM, to give 1-oxide **94** (820 mg, 90%) as a yellow powder, mp (MeOH) 208-212 °C; ^{1}H NMR δ 7.58 (d, J = 2.7 Hz, 1 H, H-8), 7.53 (d, J = 9.3 Hz, 1 H, H-5), 7.38 (dd, J = 9.3, 2.7 Hz, 1 H, H-6), 5.77 (br s, 1 H, NH), 3.91 (s, 3 H, OCH_3), 3.70-3.73 (m, 4 H, 2 × CH_2O), 3.55-3.59 (m, 2 H, CH_2N), 2.63-2.67 (m,

2 H, CH_2N), 2.48-2.52 (m, 4 H, 2 × CH_2N); ^{13}C NMR δ 158.3 (C-7), 157.3 (C-3), 145.2 (C-4a), 130.8 (C-8a), 128.9 (C-5), 127.7 (C-6), 98.2 (C-8), 66.9 (2 × CH_2O), 56.8 (CH_2N), 56.0 (OCH_3), 53.3 (2 × CH_2N), 37.5 (CH_2N); Anal. calc. for $C_{14}H_{19}N_5O_3.¼H_2O$: C, 54.3; H, 6.3; N, 22.6; found C, 54.1; H, 6.2; N, 22.8%.

Example 111

3-Chloro-7-(2-methoxyethoxy)-1,2,4-benzotriazine 1-oxide (96).

3-Hydroxy-7-(2-methoxyethoxy)-1,2,4-benzotriazine 1-oxide (95). A suspension of amine **14** (1.00 g, 4.2 mmol) in 2 N HCl (32 mL) was cooled to 5 °C and a solution of $NaNO_2$ (0.58 g, 8.5 mmol) in water (1.5 mL) was added over 1 h. More $NaNO_2$ (0.58 g, 8.5 mmol) in water (1.5 mL) was added and the suspension stirred 72 h at room temperature. The precipitate was filtered and washed with water. The solid was dissolved in 5% aqueous NH_3 and filtered. The filtrate was acidified with conc. HCl to give a precipitate which was filtered, dried and chromatographed, eluting with a gradient (0-5%) of MeOH/DCM, to give compound **95** (0.68 g, 68%) as a yellow solid, mp (DCM/pet.ether) 190-192 °C; ^1H NMR [$(CD_3)_2SO$] δ 12.52 (br, 1 H, OH), 7.69 (br s, 1 H, H-8), 7.53 (dd, *J* = 8.8, 2.8 Hz, 1 H, H-6), 7.33 (d, *J* = 8.8 Hz, 1 H, H-5), 4.19 (t, *J* = 4.4 Hz, 2 H, CH_2), 3.68 (t, *J* = 4.4 Hz, 2 H, CH_2), 3.33 (s, 3 H, OCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 154.6, 152.9, 131.8, 129.5, 127.4, 117.8, 101.8, 70.0, 67.9, 58.1; Anal. calc. for $C_{10}H_{11}N_3O_4$: C, 50.6; H, 4.2; N, 17.7; found: C, 50.5; H, 4.7; N, 17.7%.

3-Chloro-7-(2-methoxyethoxy)-1,2,4-benzotriazine 1-oxide (96). A mixture of **95** (1.00 g, 4.3 mmol) in $POCl_3$ (8 mL) was refluxed for 2 h. Excess reagent was evaporated under vacuum, and ice cold water (50 mL) was added to the residue, then solid Na_2CO_3 (1.0 g) was added portionwise. The resulting precipitate was filtered and chromatographed, eluting with a gradient (50-100%) of DCM/pet. ether, to give chloride **96** (0.90 g, 83%) as a pale yellow solid, mp (DCM/pet. ether) 121-125 °C; ^1H NMR [$(CD_3)_2SO$] δ 8.00 (d, *J* = 9.2 Hz, 1 H, H-5), 7.81 (dd, *J* = 9.2, 2.9 Hz, 1 H, H-6), 7.68 (d, *J* = 2.8 Hz, 1 H, H-8), 4.35 (t, *J* = 4.4 Hz, 2 H, CH_2), 3.74 (t, *J* = 4.4 Hz, 2 H, CH_2), 3.33 (s, 3 H, OCH_3); Anal. calc. for $C_{10}H_{10}ClN_3O_3$: C, 47.0; H, 3.9; N,16.4, Cl, 13.9; found C, 46.9; H, 4.3; N, 16.4; Cl, 13.7%.

Example 112

3-Ethyl-7-(2-methoxyethoxy)-1,2,4-benzotriazine 1-oxide (97).

$Pd(PPh_3)_4$ (92 mg, 0.08 mmol) was added to a N_2 purged solution of chloride **96** (260 mg, 1.0 mmol) and tetraethyltin (0.4 mL, 2.0 mmol) in DMF (15 mL). The purged

reaction mixture was heated at reflux temperature for 20 h under N_2. The solvent was evaporated and the residue chromatographed, eluting with 50% DCM/pet. ether, to give 1-oxide **97** (142 mg, 56%) as a white powder, mp (DCM/pet. ether) 95-97 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.97 (d, *J* = 9.2 Hz, 1 H, H-5), 7.74 (dd, *J* = 9.2, 2.9 Hz, 1 H, H-6), 7.68 (d, *J* = 2.8 Hz, 1 H, H-8), 4.33 (t, *J* = 4.4 Hz, 2 H, CH_2), 3.74 (t, *J* = 4.4 Hz, 2 H, CH_2), 3.32 (s, 3 H, OCH_3), 2.75 (q, *J* = 7.5 Hz, 2 H, CH_2), 1.33 (t, *J* = 7.6 Hz, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 164.9, 159.6, 143.1, 133.3, 129.8, 128.7, 98.1, 69.8, 68.2, 58.1, 29.5, 11.9; Anal. calc. for $C_{12}H_{15}N_3O_3$ C, 57.8; H, 6.1; N, 16.9; found C, 57.7; H, 6.1; N, 16.6%.

Example 113

3-Chloro-7-[2-(4-morpholinyl)ethoxy]-1,2,4-benzotriazine 1-oxide (98). A solution of $NaNO_2$ (286 mg, 4.1 mmol) in water (2 mL) was added slowly to a solution of amine **17** (610 mg, 2.09 mmol) in 1 N HCl (16 mL) at 5 °C. The reaction mixture was stirred at 5 °C for a further 2 h, neutralized with $NaHCO_3$ and solvent was evaporated. The residue was filtered through a short column of silica, eluting with MeOH. The filtrate was evaporated and the residue heated at reflux temperature in $POCl_3$ (2 mL) and dimethylaniline (0.6 mL, 2.5 eq) for 2 h. The reaction mixture was cooled and poured into ice/water (50 mL). The cold slurry was neutralized with solid $NaHCO_3$ (2 g), extracted with EtOAc (3 × 50 mL), dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-20%) of EtOAc/DCM, to give chloride **98** (346 mg, 53%) as a white crystals, mp (DCM/pet. ether) 144-146 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.99 (d, *J* = 9.2 Hz, 1 H, H-5), 7.80 (dd, *J* = 9.1, 2.8 Hz, 1 H, H-6), 7.70 (d, *J* = 2.8 Hz, 1 H, H-8), 4.34 (t, *J* = 5.8 Hz, 2 H, CH_2), 3.58 (t, *J* = 4.6 Hz, 4 H, 2 × CH_2), 2.77 (t, *J* = 5.5 Hz, 2 H, CH_2), 2.52-2.58 (m, 4 H, 2 × CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 160.3, 153.1, 143.1, 134.6, 129.7, 129.4, 98.7, 66.8, 66.1 (2), 56.5, 53.4 (2); Anal. calc. for $C_{13}H_{15}ClN_4O_3$: C, 50.3; H, 4.9; N,18.0; found C, 50.7; H, 5.0; N, 18.1%.

Example 114

3-Ethyl-7-[2-(4-morpholinyl)ethoxy]-1,2,4-benzotriazine 1-oxide (99). $Pd(PPh_3)_4$ (92 mg, 0.08 mmol) was added to a N_2 purged solution of chloride **96** (315 mg, 1.0 mmol) and tetraethyltin (0.4 mL, 2.0 mmol) in DMF (15 mL). The purged reaction mixture was heated at reflux temperature for 20 h under N_2. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-1%) of MeOH/DCM, to give 1-oxide **99** (204 mg, 67%) as a white powder, mp (DCM/pet.

ether) 99-101 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.96 (d, *J* = 9.0 Hz, 1 H, H-5), 7.72 (dd, *J* = 9.0, 2.8 Hz, 1 H, H-6), 7.70 (d, *J* = 2.6 Hz, 1 H, H-8), 4.36 (t, *J* = 5.8 Hz, 2 H, CH_2), 3.59 (t, *J* = 4.6 Hz, 4 H, 2 × CH_2), 2.94 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.77 (t, *J* = 5.5 Hz, 2 H, CH_2), 2.50 (t, *J* = 4.2 Hz, 4 H, 2 × CH_2),1.34 (t, *J* = 7.6 Hz, 3 H, CH_3), ^{13}C NMR [$(CD_3)_2SO$] δ 164.8, 159.5, 143.0, 133.3, 129.8, 128.8, 98.3, 66.6, 66.1 (2), 55.6, 53.5 (2), 29.5, 11.9; Anal. calc. for $C_{15}H_{20}N_4O_3$: C, 59.2; H, 6.6; N, 18.4; found C, 59.3; H, 6.5; N, 18.4%.

Example 115

3-Chloro-8-methyl-1,2,4-benzotriazine 1-oxide (100). Sodium nitrite (6.15 g, 89.1 mmol) was added in small portions to a stirred solution of 8-methyl-1,2,4-benzotriazin-3-amine 1-oxide (**3b**) (7.85 g, 44.6 mmol) in trifluoroacetic acid (80 mL) at 5 °C and the solution stirred at 20 °C for 3 h. The solution was poured into ice/water, stirred 30 minutes, filtered, washed with water (3 × 30 mL) and dried. The solid was suspended in $POCl_3$ (100 mL) and DMF (0.5 mL) and stirred at 100 °C for 1 h. The solution was cooled, poured into ice/water, stirred for 30 minutes, filtered, washed with water (3 × 30 mL) and dried. The solid was dissolved in DCM (150 mL), dried and the solvent evaporated. The residue was chromatographed, eluting with 5% EtOAc/DCM, to give chloride **100** (4.25 g, 49%) as a pale yellow solid, mp (EtOAc/DCM) 170-173 °C; ^{1}H NMR δ 7.78-7.82 (m, 2 H, H-5, H-7), 7.47-7.51 (m, 1 H, H-6), 2.98 (s, 3 H, CH_3); ^{13}C NMR δ 156.4 (C-3), 149.1 (C-4a), 135.7 (C-6), 134.5 (C-8), 133.9 (C-8a), 133.1 (C-5), 126.7 (C-7), 23.6 (CH_3); Anal. calc. for $C_8H_6ClN_3O$: C, 49.1; H, 3.1; N, 21.5; found: C, 49.4; H, 2.9; N, 21.6%.

Example 116

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(8-methyl-1-oxido-1,2,4-benzotriazin-3-yl)-1,2-ethanediamine (101).** *N*,*N*-Dimethylethanediamine (530 μL, 4.9 mmol) was added to a stirred solution of chloride **100** (316 mg, 1.6 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 2 h. The solution was cooled, the solvent evaporated and the residue partitioned between dilute aqueous NH_3 (100 mL) and DCM (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **101** (341 mg, 85%) as a yellow solid, mp (MeOH/EtOAc) 121-123 °C; ^{1}H NMR δ 7.48 (dd, *J* = 8.1, 7.1 Hz, 1 H, H-6), 7.41 (d, *J* = 8.1 Hz, 1 H, H-5), 7.00 (d, *J* = 7.1 Hz, 1 H, H-7), 5.86 (br s, 1 H, NH), 3.51-3.57 (m, 2 H, CH_2N), 2.88 (s, 3 H, CH_3), 2.56-2.60 (m, 2 H, CH_2N), 2.29 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR δ 158.5 (C-3), 150.7 (C-4a), 134.4

(C-6), 134.2 (C-8), 131.1 (C-8a), 127.5 (C-5), 124.7 (C-7), 57.6 (CH_2N), 45.0 [$N(CH_3)_2$], 38.6 (CH_2N), 24.0 (CH_3); Anal. calc. for $C_{12}H_{17}N_5O$; C, 58.3; H, 6.9; N, 28.3; found C, 58.0: H, 7.2; N, 28.1%.

Example 117

8-Methyl-*N*-[2-(1-piperidinyl)ethyl]-1,2,4-benzotriazin-3-amine 1-oxide (102). 2-(1-Piperidinyl)ethylamine (1.26 mL, 8.9 mmol) was added to a stirred solution of chloride **100** (578 mg, 3.0 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 2 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and dilute aqueous NH_3 (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **102** (764 mg, 90%) as a yellow powder, mp (MeOH/EtOAc) 137-140 °C; ^{1}H NMR δ 7.48 (dd, J = 7.8, 7.8 Hz, 1 H, H-6), 7.41 (br d, J = 7.8 Hz, 1 H, H-5), 7.00 (d, J = 7.1 Hz, 1 H, H-7), 5.90 (br s, 1 H, NH), 3.52-3.56 (m, 2 H, CH_2N), 2.90 (s, 3 H, CH_3), 2.55-2.59 (m, 2 H, CH_2N), 2.40-2.45 (m, 4 H, 2 × CH_2N), 1.55-1.61 (m, 4 H, 2 × CH_2), 1.41-1.48 (m, 2 H, CH_2); ^{13}C NMR δ 158.4 (C-3), 150.7 (C-4a), 134.5 (C-6), 134.2 (C-8), 131.1 (C-8a), 127.4 (C-5), 124.7 (C-7), 57.0 (CH_2N), 54.3 (2 × CH_2N), 37.9 (CH_2N), 26.0 (2 × CH_2), 24.4 (CH_2), 24.0 (CH_3).

Example 118

3-Chloro-6,7-dimethyl-1-oxido-1,2,4-benzotriazine (104). A mixture of 4,5-dimethyl-2-nitroaniline **103** (5.0 g, 30.1 mmol) and cyanamide (5.06 g, 120 mmol) were mixed together at 100 °C. The mixture was cooled to ca. 50 °C and cHCl (15 mL) added (CAUTION: exotherm) and the resulting solution heated at 100 °C for 1 h. The solution was cooled to ca. 50 °C and 7.5 M NaOH solution (50 mL) added carefully. The suspension was stirred at 100 °C for 2 h, cooled to 20 °C and diluted with water (100 mL). The suspension was filtered, washed with water (2 × 10 mL), washed with ether (2 × 10 mL) and dried. The yellow solid (4.50 g, 23.7 mmol) was suspended in 2 M HCl (250 mL), cooled to 5 °C, and a solution of $NaNO_2$ (3.27 g, 47.3 mmol) in water (20 mL) added dropwise. The mixture was stirred vigorously for 2 h at 20 °C. The suspension was filtered, the solid suspended in dilute aqueous NH_3 (200 mL) and filtered. The filtrate was acidified with cHCl, cooled at 5 °C for 16 h and the precipitate collected. The solid was washed with water (2 × 15 mL) and dried to give the 3-hydroxy-6,7-dimethyl-1,2,4-benzotriazine 1-oxide (1.21 g, 21%) which was used without further characterization. A mixture of the 3-hydroxide (1.21 g, 6.3 mmol), dimethylaniline (2.0 mL, 15.8 mmol) and $POCl_3$ (4.1 mL, 44.3 mmol) was

heated at reflux temperature for 1 h. The solution was poured onto ice, stirred and filtered. The solid was dissolved in EtOAc (200 mL), dried, and the solvent evaporated. The residue was chromatographed, eluting with 5% EtOAc/DCM, to give the chloride **104** (1.07 g, 81%) as colourless plates, mp 148-149 °C; ^{1}H NMR δ 8.16 (s, 1 H, H-8), 7.72 (s, 1 H, H-5), 2.51 (s, 3 H, CH_3), 2.50 (s, 3 H, CH_3); ^{13}C NMR δ 156.1 (C-3), 148.9 (C-6), 146.3 (C-4a), 142.5 (C-7), 132.0 (C-8a), 127.4 (C-5), 119.8 (C-8), 20.8 (CH_3), 20.5 (CH_3); Anal. calc. for $C_9H_8ClN_3O$: C, 51.6; H, 3.85; N, 20.0; found C, 51.8; H, 3.7; N, 20.2%

Example 119

***tert*-Butyl 2-[(6,7-dimethyl-1-oxido-1,2,4-benzotriazin-3-yl)amino]ethylcarbamate (105).** A solution of chloride **104** (842 mg, 4.0 mmol) and *tert*-butyl 2-aminoethylcarbamate (1.4 g, 8.8 mmol) in DME (50 mL) was heated at reflux temperature for 3 h. The solvent was evaporated and the residue partitioned between EtOAc (100 mL) and water (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (20-50%) of EtOAc/DCM, to give 1-oxide **105** (1.04 g, 78%) as a yellow solid, mp (EtOAc/DCM) 226-228 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.90 (s, 1 H, H-8'), 7.66 (br s, 1 H, NH), 7.39 (s, 1 H, H-5'), 6.88 (t, J = 5.3 Hz, 1 H, NH), 3.33-3.38 (m, 2 H, CH_2N), 3.14-3.18 (m, 2 H, CH_2N), 2.36 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 1.37 [$C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 155.8 ($NHCO_2$), 155.6 (C-3'), 147.1 (C-4a'), 147.8 (C-7'), 134.8 (C-6'), 128.2 (C-8a'), 125.2 (C-5'), 118.5 (C-8'), 77.6 [$\underline{C}(CH_3)_3$], 40.9 (CH_2N), 39.0 (CH_2N), 28.1 [$C(\underline{C}H_3)_3$], 19.9 (CH_3), 19.2 (CH_3); Anal. calc. for $C_{16}H_{23}N_5O_3$: C, 57.6; H, 7.0; N, 21.0; found C, 57.9; H, 7.0; N, 20.8%.

Example 120

***N*^{1}-(6,7-Dimethyl-1-oxido-1,2,4-benzotriazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (106).** *N*,*N*-Dimethyl-1,2-ethanediamine (0.3 mL, 2.7 mmol) was added to a stirred solution of chloride **104** (190 mg, 0.9 mmol) in DME (30 mL) and the solution stirred at reflux temperature for 16 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and dilute aqueous NH_3 (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give amine **106** (181 mg, 76%), mp (MeOH) 175-178 °C; ^{1}H NMR δ 8.00 (s, 1 H, H-8), 7.36 (s, 1 H, H-5), 5.82 (br s, 1 H, NH), 3.52-3.56 (m, 2 H, CH_2N), 2.55-2.59 (m, 2 H, CH_2N), 2.38 (s, 3 H, CH_3), 2.36 (s, 3 H, CH_3), 2.27 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR [$(CD_3)_2SO$] δ 158.9

(C-3), 147.8 (C-4a), 146.9 (C-6), 135.4 (C-7), 129.1 (C-8a), 125.7 (C-5), 119.4 (C-8), 57.6 (CH_2N), 45.1 [$N(CH_3)_2$], 38.7 (CH_2N), 20.5 (CH_3), 19.8 (CH_3); MS (EI) *m/z* 261 (M^+, 5%), 224 (3), 217 (1), 58 (100); HRMS calc. for $C_{13}H_{19}N_5O$ (M^+) *m/z* 261.1590, found 261.1587.

Example 121

3-Chloro-6,8-dimethyl-1,2,4-benzotriazine 1-oxide (108). A mixture 3,5-dimethyl-2-nitroaniline (**107**) (Andrews et. al., *Aust. J. Chem.* **1972**, *25*, 639) (6.61 g, 39.8 mmol) and cyanamide (6.7 g, 159 mmol) were mixed together at 100 °C, cooled to 50 °C, cHCl (30 mL) added carefully and the mixture heated at 100 °C for 4 h. The mixture was cooled to 50 °C, 7.5 M NaOH solution added until the mixture was strongly basic and the mixture stirred at 100 °C for 3 h. The mixture was cooled, diluted with water (100 mL), filtered, washed with water (3 × 30 mL), washed with ether (3 × 20 mL) and dried to give crude 1-oxide (2.62 g, 35%) as a yellow powder. Sodium nitrite (1.55 g, 22.5 mmol) was added in small portions to a stirred solution of 1-oxide (2.14 g, 11.3 mmol) in trifluoroacetic acid (20 mL) at 5 °C and the solution stirred at 20 °C for 3 h. The solution was poured into ice/water, stirred 30 minutes, filtered, washed with water (3 × 30 mL) and dried. The solid was suspended in $POCl_3$ (50 mL) and DMF (0.2 mL) stirred at 100 °C for 1 h. The solution was cooled, poured into ice/water, stirred for 30 minutes, filtered, washed with water (3 × 30 mL) and dried. The solid was suspended in DCM (150 mL), dried and the solvent evaporated. The residue was chromatographed, eluting with 5% EtOAc/DCM, to give chloride **108** (1.58 g, 67%) as a pale yellow solid, mp (EtOAc/DCM) 120-122 °C; ^{1}H NMR δ 7.55 (s, 1 H, H-5), 7.30 (s, 1 H, 1 H, H-7), 2.93 (s, 3 H, CH_3), 2.52 (s, 3 H, CH_3); ^{13}C NMR δ 156.4 (C-3), 149.4 (C-4a), 147.7 (C-6), 135.1 (C-5), 133.9 (C-8), 132.2 (C-8a), 125.5 (C-7), 23.4 (CH_3), 21.9 (CH_3); Anal. calc. for $C_9H_8ClN_3O$: C, 51.6; H, 3.9; N, 20.0; Cl, 16.9; found C, 51.8; H, 3.6; N, 20.2; Cl, 16.6%.

Example 122

***N*^{1}-(6,8-Dimethyl-1-oxido-1,2,4-benzotriazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (109).** *N,N*-Dimethylethanediamine (0.64 mL, 5.9 mmol) was added to a stirred solution of chloride **108** (494 mg, 2.4 mmol) in DME (80 mL) and the solution stirred at reflux temperature for 2 h. The solution was cooled, the solvent evaporated and the residue partitioned between dilute aqueous NH_3 (100 mL) and DCM (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to

give 1-oxide **109** (561 mg, 91%) as a yellow solid, mp (MeOH) 176-179 °C; ^{1}H NMR δ 7.20 (br s, 1 H, H-5), 6.84 (br s, 1 H, H-7), 5.76 (br s, 1 H, NH), 3.50-3.54 (m, 2 H, CH_2N), 2.85 (s, 3 H, CH_3), 2.52-2.56 (m, 2 H, CH_2N), 2.38 (s, 3 H, CH_3), 2.26 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR δ 158.7 (C-3), 150.9 (C-4a), 145.6 (C-6), 133.7 (C-8), 129.6 (C-5), 129.4 (C-8a), 123.7 (C-7), 57.6 (CH_2N), 45.1 [$N(CH_3)_2$], 38.7 (CH_2N), 23.8 (CH_3), 21.6 (CH_3); Anal. calc. for $C_{13}H_{19}N_5O$; C, 59.8; H, 7.3; N, 26.8; found C, 60.0: H, 7.6; N, 27.0%.

Example 123

6,8-Dimethyl-*N*-[2-(1-piperidinyl)ethyl]-1,2,4-benzotriazin-3-amine 1-oxide (110). 2-(1-Piperidinyl)ethylamine (0.67 mL, 4.7 mmol) was added to a stirred solution of chloride **108** (395 mg, 1.9 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 2 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and dilute aqueous NH_3 (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-5%) of MeOH/DCM, to give 1-oxide **110** (517 mg, 91%) as a yellow powder, mp (MeOH) 177-178 °C; ^{1}H NMR δ 7.20 (s, 1 H, H-5), 6.84 (s, 1 H, H-7), 5.84 (br s, 1 H, NH), 3.49-3.55 (m, 2 H, CH_2N), 2.85 (s, 3 H, CH_3), 2.54-2.57 (m, 2 H, CH_2N), 2.39-2.44 (m, 4 H, 2 × CH_2N), 2.37 (s, 3 H, CH_3), 1.55-1.61 (m, 4 H, 2 × CH_2), 1.41-1.47 (m, 2 H, CH_2); ^{13}C NMR δ 158.6 (C-3), 150.9 (C-4a), 145.6 (C-6), 133.7 (C-8), 129.5 (C-5), 129.4 (C-8a), 123.7 (C-7), 57.0 (CH_2N), 54.3 (2 × CH_2N), 37.9 (CH_2N), 26.0 (2 × CH_2), 24.4 (CH_2), 23.8 (CH_3), 21.7 (CH_3); Anal. calc. for $C_{16}H_{23}N_5O$: C, 63.8; H, 7.7; N, 23.2; found C, 63.9; H, 8.0; N, 23.5%.

Example 124

6-Methoxy-7-methyl-1,2,4-benzotriazin-3-amine 1-oxide (112). A mixture of 5-methoxy-4-methyl-2-nitroaniline (**111**) (James & Felix, *U.S. Patent* 5,360,986) (8.9 g, 49 mmol) and cyanamide (8.2 g, 196 mmol) were mixed together at 100 °C, cooled to 50 °C, cHCl (50 mL) added carefully and the mixture heated at 100 °C for 4 h. The mixture was cooled to 50 °C, 7.5 M NaOH solution added until the mixture was strongly basic and the mixture stirred at 100 °C for 3 h. The mixture was cooled, diluted with water (200 mL), filtered, washed with water (3 × 50 mL), washed with ether (3 × 30 mL) and dried. The solid was recrystallized from MeOH to give 1-oxide **112** (6.0 g, 59%) as a yellow powder, mp (MeOH) 289-292 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.91 (d, J = 1.1 Hz, 1 H, H-8), 7.10 (br s, 2 H, NH_2), 6.84 (s, 1 H, H-5), 3.94 (s, 3 H, OCH_3), 2.23 (s, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 163.7 (C-6), 160.4 (C-3), 150.3 (C-

4a), 127.3 (C-7), 124.4 (C-8a), 120.0 (C-8), 102.7 (C-5), 56.3 (OCH_3), 16.1 (CH_3); Anal. calc. for $C_9H_{10}N_4O_2.¼MeOH$: C, 51.9; H, 5.2; N, 26.2; found C, 52.1; H, 4.8; N, 26.4%.

Example 125

3-Chloro-6-methoxy-7-methyl-1,2,4-benzotriazine 1-oxide (113). Sodium nitrite (3.38 g, 49.0 mmol) was added in small portions to a stirred solution of 1-oxide **112** (5.05 g, 24.5 mmol) in trifluoroacetic acid (30 mL) at 5 °C and the solution stirred at 20 °C for 3 h. The solution was poured into ice/water, stirred 30 minutes, filtered, washed with water (3 × 30 mL) and dried. The solid was suspended in $POCl_3$ (50 mL) and DMF (0.2 mL) stirred at 100 °C for 1 h. The solution was cooled, poured into ice/water, stirred for 30 minutes, filtered, washed with water (3 × 30 mL) and dried. The solid was suspended in DCM (150 mL), dried and the solvent evaporated. The residue was chromatographed, eluting with 5% EtOAc/DCM, to give chloride **113** (2.72 g, 49%) as a pale yellow solid, mp (EtOAc) 180-182 °C; ^{1}H NMR δ 8.44 (d, *J* = 0.9 Hz, 1 H, H-8), 7.14 (s, 1 H, 1 H, H-5), 4.03 (s, 3 H, OCH_3), 2.40 (d, *J* = 0.9 Hz, 3 H, CH_3); ^{13}C NMR δ 165.4 (C-6), 156.8 (C-3), 149.2 (C-4a), 135.5 (C-7), 128.4 (C-8a), 120.4 (C-8), 104.3 (C-5), 56.6 (OCH_3), 17.2 (CH_3); Anal. calc. for $C_9H_8ClN_3O_2$: C, 47.9; H, 3.6; N, 18.6; Cl, 15.7; found C, 48.0; H, 3.5; N, 18.6; Cl, 15.7%.

Example 126

***N*^{1}-(6-Methoxy-7-methyl-1-oxido-1,2,4-benzotriazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (114).** *N*,*N*-Dimethylethanediamine (0.70 mL, 6.3 mmol) was added to a stirred solution of chloride **113** (474 mg, 2.1 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 2 h. The solution was cooled, the solvent evaporated and the residue partitioned between dilute aqueous NH_3 (100 mL) and DCM (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-15%) of MeOH/DCM, to give 1-oxide **114** (529 mg, 90%) as a yellow solid, mp (MeOH) 167-169 °C; ^{1}H NMR δ 7.99 (d, *J* = 1.0 Hz, 1 H, H-8'), 6.79 (s, 1 H, H-5'), 5.84 (br s, 1 H, NH), 3.94 (s, 3 H, OCH_3), 3.49-3.54 (m, 2 H, CH_2N), 2.52-2.56 (m, 2 H, CH_2N), 2.27 (d, *J* = 1.0 Hz, 3 H, CH_3), 2.26 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR δ 164.5 (C-6'), 159.3 (C-3'), 150.5 (C-4a'), 128.5 (C-7'), 125.4 (C-8a'), 120.7 (C-8'), 120.7 (C-5'), 57.5 (CH_2N), 56.1 (OCH_3), 45.1 [$N(CH_3)_2$], 38.7 (CH_2N), 16.5 (CH_3); Anal. calc. for $C_{13}H_{19}N_5O_2$: C, 56.3; H, 6.9; N, 25.3; found C, 56.5: H, 7.2; N, 25.7%.

Example 127

7-Methoxy-6-methyl-1,2,4-benzotriazin-3-amine 1-oxide (116). A mixture of 4-methoxy-5-methyl-2-nitroaniline (**115**) (Arnold & McCool, *J. Am. Chem. Soc.* **1942**, *64*, 1315) (2.3 g, 12.6 mmol) and cyanamide (2.0 g, 50 mmol) were mixed together at 100 °C, cooled to 50 °C, cHCl (20 mL) added carefully and the mixture heated at 100 °C for 4 h. The mixture was cooled to 50 °C, 7.5 M NaOH solution added until the mixture was strongly basic and the mixture stirred at 100 °C for 3 h. The mixture was cooled, diluted with water (100 mL), filtered, washed with water (3 × 30 mL), washed with ether (3 × 20 mL) and dried to give crude 1-oxide **116** (2.52 g, 97%) as a yellow powder, mp (MeOH) >320 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.42 (s, 1 H, H-8), 7.39 (d, J = 1.0 Hz, 1 H, H-5), 6.99 (br s, 2 H, NH_2), 3.90 (s, 3 H, OCH_3), 2.30 (s, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 159.7 (C-7), 155.4 (C-3), 144.8 (C-4a), 139.3 (C-6), 128.4 (C-8a), 126.2 (C-5), 96.6 (C-8), 56.0 (OCH_3), 16.7 (CH_3).

Example 128

3-Chloro-7-methoxy-6-methyl-1,2,4-benzotriazine 1-oxide (117). Sodium nitrite (1.7 g, 24.4 mmol) was added in small portions to a stirred solution of 1-oxide **116** (2.50 g, 12.2 mmol) in trifluoroacetic acid (20 mL) at 5 °C and the solution stirred at 20 °C for 3 h. The solution was poured into ice/water, stirred 30 minutes, filtered, washed with water (3 × 30 mL) and dried. The solid was suspended in $POCl_3$ (50 mL) and DMF (0.2 mL) stirred at 100 °C for 1 h. The solution was cooled, poured into ice/water, stirred for 30 minutes, filtered, washed with water (3 × 30 mL) and dried. The solid was suspended in DCM (150 mL), dried and the solvent evaporated. The residue was chromatographed, eluting with 5% EtOAc/DCM, to give chloride **117** (1.38 g, 50%) as a pale yellow solid, mp (EtOAc/DCM) 200-202 °C; ^{1}H NMR δ 7.70 (d, J = 0.9 Hz, 1 H, H-5), 7.59 (s, 1 H, 1 H, H-8), 4.03 (s, 3 H, OCH_3), 2.44 (d, J = 0.9 Hz, 3 H, CH_3); ^{13}C NMR δ 160.7 (C-7), 154.7 (C-3), 143.5 (C-4a), 142.0 (C-6), 133.1 (C-8a), 128.4 (C-5), 96.4 (C-8), 56.6 (OCH_3), 17.4 (CH_3); Anal. calc. for $C_9H_8ClN_3O_2$: C, 47.9; H, 3.6; N, 18.6; found C, 48.1; H, 3.4; N, 18.7%.

Example 129

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(7-methoxy-6-methyl-1-oxido-1,2,4-benzotriazin-3-yl)-1,2-ethanediamine (118).** *N,N*-Dimethylethanediamine (0.48 mL, 4.3 mmol) was added to a stirred solution of chloride **117** (391 mg, 1.7 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 2 h. The solution was cooled, the solvent evaporated and the residue partitioned between dilute aqueous NH_3 (100 mL) and

DCM (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **118** (432 mg, 90%) as a yellow solid, mp (MeOH/EtOAc) 182-184 °C; ^{1}H NMR δ 7.49 (s, 1 H, H-8'), 7.36 (s, 1 H, H-5'), 5.72 (br s, 1 H, NH), 3.92 (s, 3 H, OCH_3), 3.49-3.54 (m, 2 H, CH_2N), 2.53-2.56 (m, 2 H, CH_2N), 2.34 (s, 3 H, CH_3), 2.26 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR δ 158.6 (C-7'), 156.4 (C-3'), 145.2 (C-4a'), 140.2 (C-6'), 129.4 (C-8a'), 124.9 (C-5'), 96.9 (C-8'), 57.6 (CH_2N), 56.0 (OCH_3), 45.1 [$N(CH_3)_2$], 38.8 (CH_2N), 17.2 (CH_3); Anal. calc. for $C_{13}H_{19}N_5O_2$: C, 56.3; H, 6.9; N, 25.3; found C, 56.5: H, 6.7; N, 25.5%.

Example 130

7-Methoxy-6-methyl-*N*-[2-(1-piperidinyl)ethyl]-1,2,4-benzotriazin-3-amine 1-oxide (119). 2-(1-Piperidinyl)ethylamine (0.74 mL, 5.2 mmol) was added to a stirred solution of chloride **117** (467 mg, 2.1 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 4 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and dilute aqueous NH_3 (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-5%) of MeOH/DCM, to give 1-oxide **119** (574 mg, 87%) as a yellow powder, mp (MeOH/EtOAc) 195-197 °C; ^{1}H NMR δ 7.50 (s, 1 H, H-8), 7.36 (d, J = 0.8 Hz, 1 H, H-5), 5.83 (br s, 1 H, NH), 3.92 (s, 3 H, OCH_3), 3.49-3.54 (m, 2 H, CH_2N), 2.54-2.59 (m, 2 H, CH_2N), 2.39-2.43 (m, 4 H, 2 × CH_2N), 2.33 (s, 3 H, CH_3), 1.54-1.60 (m, 4 H, 2 × CH_2), 1.41-1.47 (m, 2 H, CH_2); ^{13}C NMR δ 158.6 (C-7), 156.3 (C-3), 145.2 (C-4a), 140.2 (C-6), 129.4 (C-8a), 126.8 (C-5), 96.9 (C-8), 57.0 (CH_2N), 56.0 (OCH_3), 54.3 (2 × CH_2N), 38.0 (CH_2N), 26.0 (2 × CH_2), 24.4 (CH_2), 17.2 (CH_3); Anal. calc. for $C_{16}H_{23}N_5O_2$: C, 60.6; H, 7.3; N, 22.1; found C, 60.6; H, 7.1; N, 22.3%.

Example 131

***N*-(2-{2-[(1-Oxido-1,2,4-benzotriazin-3-yl)amino]ethoxy}ethyl)-4-acridinecarboxamide (121).** A solution of amine **36** (0.53 g, 2.1 mmol) in DCM (10 mL) was added dropwise to a stirred solution of imidazolide of acridine-4-carboxylic acid **120** (0.58 g, 2.1 mmol) in THF (25 mL) and the solution stirred at 20 °C for 72 h. The solvent was evaporated and the residue chromatographed, eluting with a gradiant (0-4%) of MeOH/DCM, to give **121** (642 mg, 66%) as a yellow powder, mp 178-182 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.75 (t, J = 5.0 Hz, 1 H, NH), 9.27 (s, 1 H, H-9), 8.74 (dd, J = 8.4, 1.5 Hz, 1 H, H-3), 8.36 (dd, J = 8.4, 1.4 Hz, 1 H, H-1), 8.18 (m, 2 H, H-5, H-8), 8.02 (dd, J = 8.6, 1.2 Hz, 1 H, H-8'), 7.90 (br s, 1 H, NH), 7.83 (t, J = 7.5

Hz, 1 H, H-6), 7.75 (dd, J = 8.6, 7.2 Hz, 1 H, H-2), 7.70 (ddd, J = 8.6, 7.1, 1.2 Hz, 1 H, H-6'), 7.61 (ddd, J = 8.9, 7.1, 0.7 Hz, 1 H, H-7), 7.42 (br d, J = 8.6 Hz, 1 H, H-5'), 7.28 (ddd, J = 8.4, 7.1, 1.4 Hz, 1 H, H-7'), 3.80-3.84 (m, 4 H, 2 × CH_2O), 3.73-3.77 (m, 2 H, CH_2N), 3.60-3.65 (m, 2 H, CH_2N); ^{13}C NMR [$(CD_3)_2SO$] δ 164.6 (CONH), 158.8 (C-3'), 148.0 (C-4a'), 146.8 (C-4b), 145.3 (C-4a), 138.5 (C-9), 135.5 (C-6'), 134.5 (C-3), 132.8 (C-1), 131.7 (C-6), 129.9 (C-9a, C-8a'), 128.3 (C-8), 128.2 (C-5), 127.9 (C-7), 126.3 (C-5'), 125.8 (C-4), 125.5 (C-8a), 125.1 (C-7'), 124.4 (C-2), 119.7 (C-8'), 69.0 (CH_2O), 68.4 (CH_2O), 40.5 (CH_2N), 39.1 (CH_2N); Anal. calc. for $C_{25}H_{22}N_6O_3.½H_2O$: C, 64.8; H, 5.0; N, 18.1; found C, 65.2; H, 4.8; N, 18.4%.

Example 132

3-[(2-Methoxyethyl)amino]-2-quinoxalinecarbonitrile 1-oxide (123). 2-Methoxyethylamine (0.32 mL, 3.0 mmol) was added to a stirred solution of 3-chloro-2-quinoxalinecarbonitrile 1-oxide **122** (Yoshida & Otomasu, *Chem. Pharm. Bull.* **1984**, *32*, 3361) (203 mg, 1.0 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 2 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and dilute aqueous NH_3 (50 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with 5% EtOAc/DCM, to give 1-oxide **123** (209 mg, 86%) as a yellow powder, mp (MeOH) 124-126 °C; ^1H NMR δ 8.28 (br d, J = 8.5 Hz, 1 H, H-8), 7.66-7.71 (m, 2 H, H-5, H-6), 7.36-7.42 (m, 1 H, H-7), 5.60 (br s, 1 H, NH), 3.78-3.84 (m, 2 H, CH_2N), 3.63-3.66 (m, 2 H, CH_2O), 3.42 (s, 3 H, OCH_3); ^{13}C NMR δ 154.2 (C-3), 144.6 (C-4a), 134.1 (C-6), 132.6 (C-8a), 127.6 (C-5), 125.7 (C-7), 118.9 (C-8), 111.9 (C-2), 108.2 (CN), 70.4 (CH_2O), 59.0 (OCH_3), 41.2 (CH_2N); Anal. calc. for $C_{12}H_{12}N_4O_2$: C, 59.0; H, 5.0; N, 22.9; found C, 59.2; H, 5.2; N, 22.6%.

Example 133

1,2,4-Benzotriazine 1-oxide (124). Isoamyl nitrite (1.05 mL, 7.8 mmol) was added to a stirred solution of 1-oxide **3** (254 mg, 1.6 mmol) in DMF (10 mL) and the solution stirred at 60 °C for 2 h. The solvent was evaporated and the residue partitioned between EtOAc (50 mL) and water (50 mL). The organic fraction was washed with water (2 × 25 mL), brine (20 mL), dried, and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of EtOAc/DCM, to give **124** (120 mg, 52%) as a pale yellow solid, mp (EtOAc/DCM) 138-139 °C [lit. (Robbins & Schofield, *J. Chem. Soc.* **1957**, 3186) mp (MeOH) 138-140 °C]; ^1H NMR δ 9.19 (s, 1

H, H-3), 8.41 (d, *J* = 8.6 Hz, 1 H, H-8), 8.10-8.13 (m, 2 H, H-5, H-6), 7.90-7.94 (m, 1 H, H-7).

Examples 134 and 135

1,2,4-Benzotriazin-3-amine 2-oxide (126) and 1,2,4-benzotriazin-3-amine 4-oxide (127).

1,2,4-Benzotriazin-3-amine (125). A solution of 1-oxide **3** (1.98 g, 14.3 mmol) and $Na_2S_2O_4$ (4.99 g, 28.7 mmol) in 70% aqueous EtOH (100 mL) was heated at reflux temperature for 3 h. The hot suspension was filtered and the filtrate extracted with $CHCl_3$ (3 × 50 mL). The combined organic fraction was dried and the solvent evaporated. The combined solid and extracts were chromatographed, eluting with a gradient (0-2%) of MeOH/$CHCl_3$, to give benzotriazine **125** (1.58 g, 67%) as a yellow solid, mp ($CHCl_3$/MeOH) 200-203 °C [lit. (Mason & Tennant, *J. Chem. Soc. (B)* **1970**, 911) mp 207 °C]; ^{1}H NMR δ 8.19 (dd, *J* = 8.3, 0.9 Hz, 1 H, H-8), 7.78-7.83 (m, 1 H, H-6), 7.62 (br s, 2 H, NH_2), 7.54 (d, *J* = 8.4 Hz, 1 H, H-5), 7.43-7.48 (m, 1 H, H-7).

1,2,4-Benzotriazin-3-amine 2-oxide (126) and 1,2,4-benzotriazin-3-amine 4-oxide (127). A solution of MCPBA (0.89 g, 3.6 mmol) in DCM (5 mL) was added dropwise to a stirred solution of **125** (0.50 g, 3.4 mmol) in 10% MeOH/DCM (50 mL) at 20 °C and the solution stirred at 20 °C for 3 h. The solution was washed with dilute aqueous NH_3 solution (50 mL), dried, and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-5%) of MeOH/$CHCl_3$, to give (i) 1,2,4-benzotriazin-3-amine 2-oxide (**126**) (405 mg, 70%) as a yellow powder, mp (MeOH/DCM) 175-180 °C [lit. (Mason & Tennant, *J. Chem. Soc. (B)* **1970**, 911) mp (HOAc) 200 °C]; ^{1}H NMR δ 8.20 (br s, 2 H, NH_2), 7.68 (d, *J* = 8.2 Hz, 1 H, H-8), 7.60-7.65 (m, 1 H, H-6), 7.53 (d, *J* = 7.6 Hz, 1 H, H-5), 7.45-7.59 (m, 1 H, H-7); followed by (ii) 1,2,4-benzotriazin-3-amine 1-oxide (**3**) (65 mg, 11%) as a yellow powder, mp 266-268 °C [lit. (Arndt, *Ber.* **1913**, *46*, 3522) mp (EtOH) 269 °C]; spectroscopically identical with the sample prepared above; and (iii) 1,2,4-benzotriazin-3-amine 4-oxide (**127**) (51 mg, 9%) as pale yellow solid, [lit. (Fuchs, et. al., *J. Org. Chem.* **2001**, *66*, 107)]; ^{1}H NMR δ 8.29 (d, *J* = 8.6 Hz, 1 H, H-8), 8.20 (br s, 2 H, NH_2), 8.16 (d, *J* = 8.6 Hz, 1 H, H-5), 7.91 (ddd, *J* = 8.6, 7.0, 1.2 Hz, 1 H, H-6), 7.65 (ddd, *J* = 8.6, 7.0, 1.1 Hz, 1 H, H-7); MS (EI) 162 (M^+, 100%), 146 (10); HRMS (EI) calc. for $C_7H_6N_4O$ (M^+) *m/z* 162.0542, found 162.0540.

Example 136

***tert*-Butyl bis{3-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]propyl}carbamate (129).** A solution of chloride **19** (0.86 g, 4.8 mmol), Et_3N (1.0 mL, 7.1 mmol) and *tert*-butyl bis(3-aminopropyl)carbamate (1.1 g, 4.8 mmol) in DCM was stirred at 20 °C for 3 days. The solvent was evaporated and the residue chromatographed, eluting with 20% EtOAc/DCM, to give bis-1-oxide **129** (457 mg, 18%) as a yellow oil, ^{1}H NMR δ 8.24 (d, *J* = 8.4 Hz, 2 H, 2 × H-8'), 7.65-7.69 (m, 2 H, 2 × H-6'), 7.56 (br d, *J* = 8.5 Hz, 2 H, 2 × H-5'), 7.23-7.28 (m, 2 H, 2 × H-7'), 6.26 (br s, 2 H, 2 × NH), 3.54-3.57 (m, 4 H, 2 × CH_2N), 2.32-2.39 (m, 4 H, 2 × CH_2N), 1.85-1.93 (m, 4 H, 2 × 2 × CH_2), 1.49 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 158.9 (2 × C-3'), 156.1 (NCO_2), 148.9 (2 × C-4a'), 135.4 (2 × C-6'), 130.9 (2 × C-8a'), 126.4 (2 × C-5'), 124.9 (2 × C-7'), 120.4 (2 × C-8'), 80.2 [$O\underline{C}(CH_3)_3$], 60.4 (2 × CH_2N), 46.0 (2 × NCH_2), 28.5 (2 × CH_2), 28.4 [$OC(\underline{C}H_3)_3$]; Anal. calc. for $C_{25}H_{31}N_9O_4$: C, 57.6; H, 6.0; found C, 57.1; H, 6.1%.

Example 137

***N*^{1}-Methyl-*N*^{2}-(1-oxido-1,2,4-benzotriazin-3-yl)-1,2-ethanediamine (130).** *N*-Methylethanediamine (0.73 mL, 8.3 mmol) was added to a stirred solution of chloride **19** (1.0 g, 5.5 mmol) and Et_3N (1.2 mL, 8.3 mmol) in DCM (50 mL) and the solution stirred at 20 °C for 2 days. The solution was cooled, the solvent evaporated and the residue partitioned between dilute aqueous NH_3 (100 mL) and DCM (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give 1-oxide **130** (600 mg, 50%) as a yellow solid, mp (MeOH/EtOAc) 226-228 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.40 (br s, 1 H, NH), 8.17 (dd, *J* = 8.6, 1.0 Hz, 1 H, H-8'), 7.84 (ddd, *J* = 8.4, 7.0, 1.0 Hz, 1 H, H-6'), 7.64 (br d, *J* = 8.4 Hz, 1 H, H-5'), 7.40 (ddd, *J* = 8.6, 7.0, 1.0 Hz, 1 H, H-7'), 3.93-3.97 (m, 2 H, CH_2N), 3.53 [br s, 1 H, NH), 3.21 (s, 3 H, NCH3), 3.13-3.17 (m, 2 H, CH_2N); ^{13}C NMR [$(CD_3)_2SO$] δ 158.3 (C-3'), 148.2 (C-4a'), 135.9 (C-6'), 129.3 (C-8a'), 126.2 (C-5'), 125.2 (C-7'), 119.8 (C-8'), 45.5 (CH_2N), 36.7 (CH_2N), 35.6 (NCH_3).

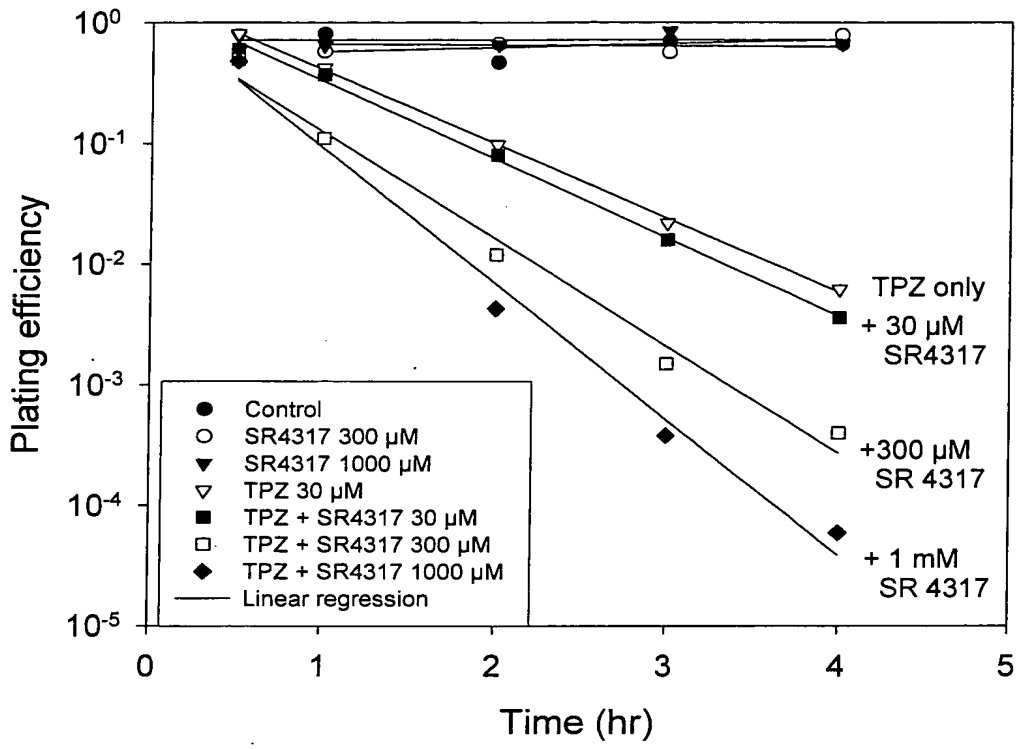
Wherein the foregoing description reference has been made to reagents or integers having known equivalents thereof, then those equivalents are herein incorporated as if individually set forth.

While this invention has been described with reference to certain embodiments and examples, it is to be appreciated that further modifications and variations may be made thereto without departing from the spirit or scope of the invention.

AUCKLAND UNISERVICES LIMITED

By Its Attorneys
BALDWIN SHELSTON WATERS

Figure 1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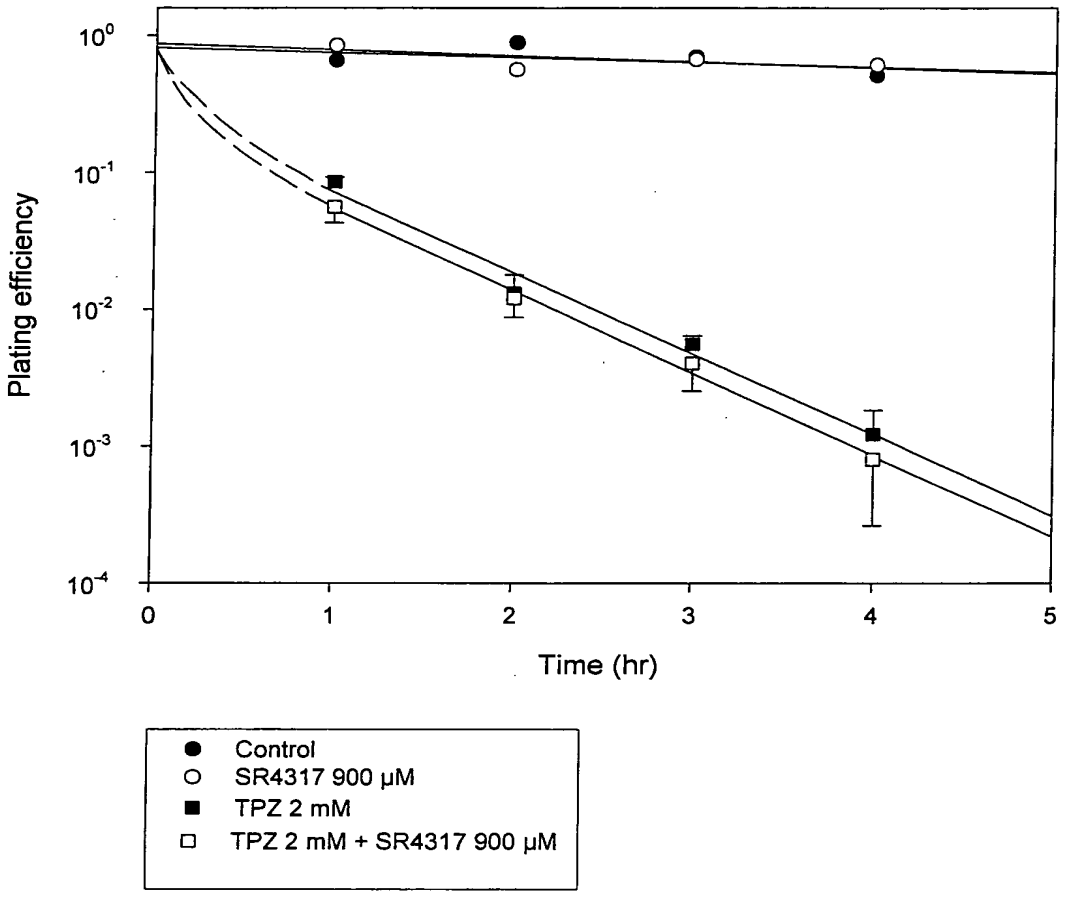
10^{-2}
10^{-3}
10^{-4}
10^{-5}
0
1
2
3
4
5
Time (hr)
Control
SR4317 300 µM
SR4317 1000 µM
TPZ 30 µM
TPZ + SR4317 30 µM
TPZ + SR4317 300 µM
TPZ + SR4317 1000 µM
Linear regression
TPZ only
+ 30 µM SR4317
+300 µM SR 4317
+ 1 mM SR 4317

Figure 2


Plating efficiency
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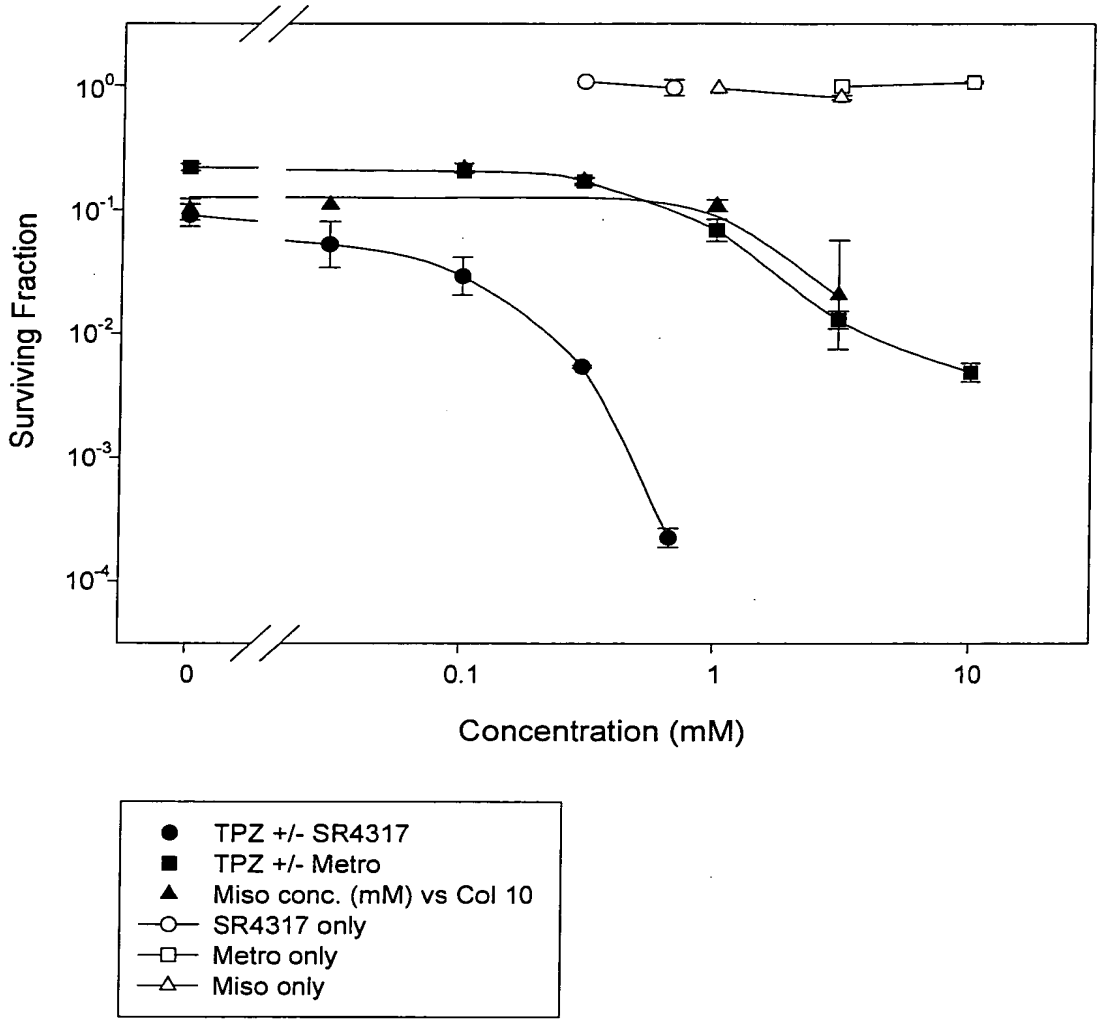
10^{-1}
10^{-2}
10^{-3}
10^{-4}
0
1
2
3
4
5
Time (hr)
Control
SR4317 900 µM
TPZ 2 mM
TPZ 2 mM + SR4317 900 µM

Figure 3.


Surviving Fraction
10^0
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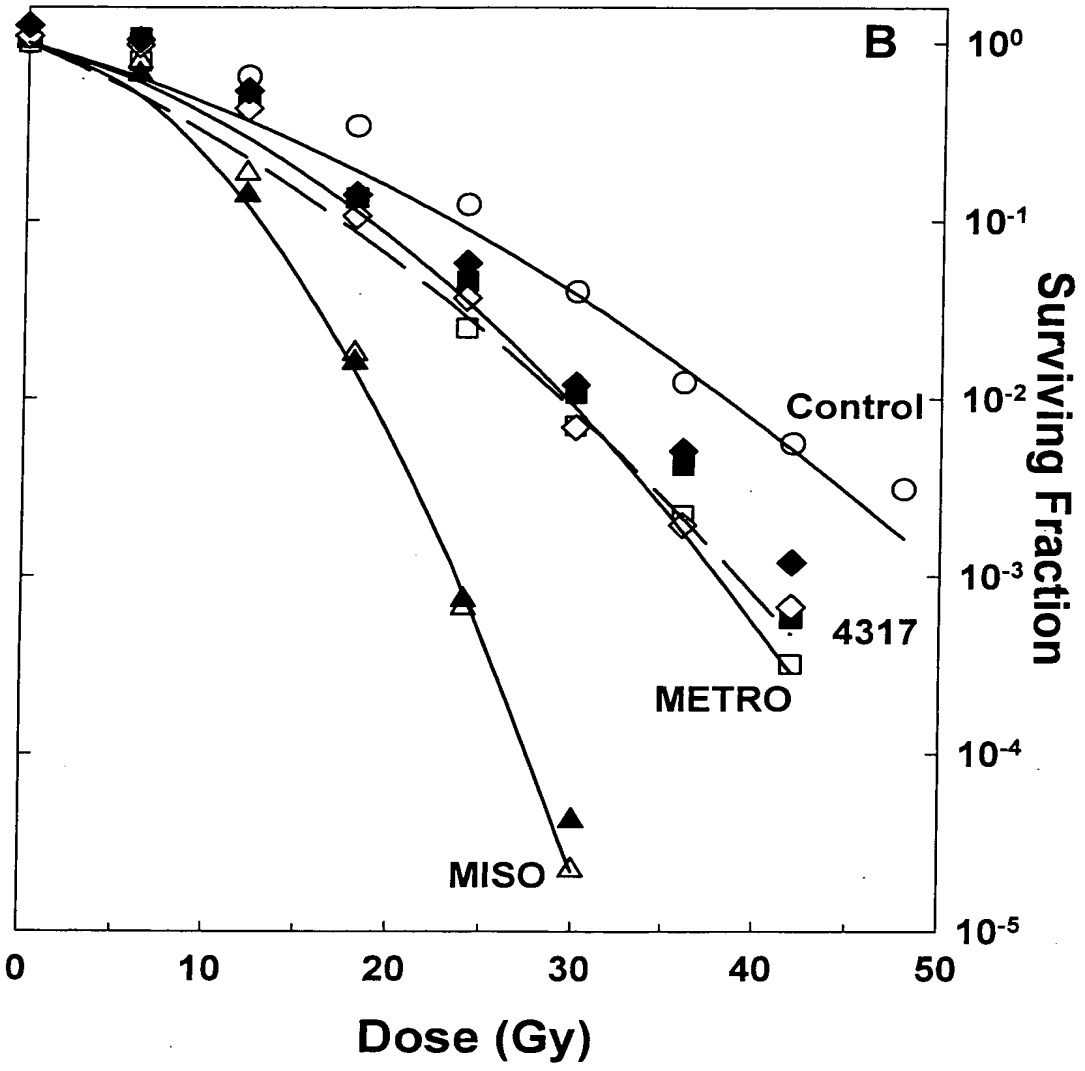
10^{-2}
10^{-3}
10^{-4}
0
0.1
1
10
Concentration (mM)
TPZ +/- SR4317
TPZ +/- Metro
Miso conc. (mM) vs Col 10
SR4317 only
Metro only
Miso only

Figure 4 :


B
Control
4317
METRO
MISO
Surviving Fraction
Dose (Gy)
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10^-2
10^-3
10^-4
10^-5
0
10
20
30
40
50

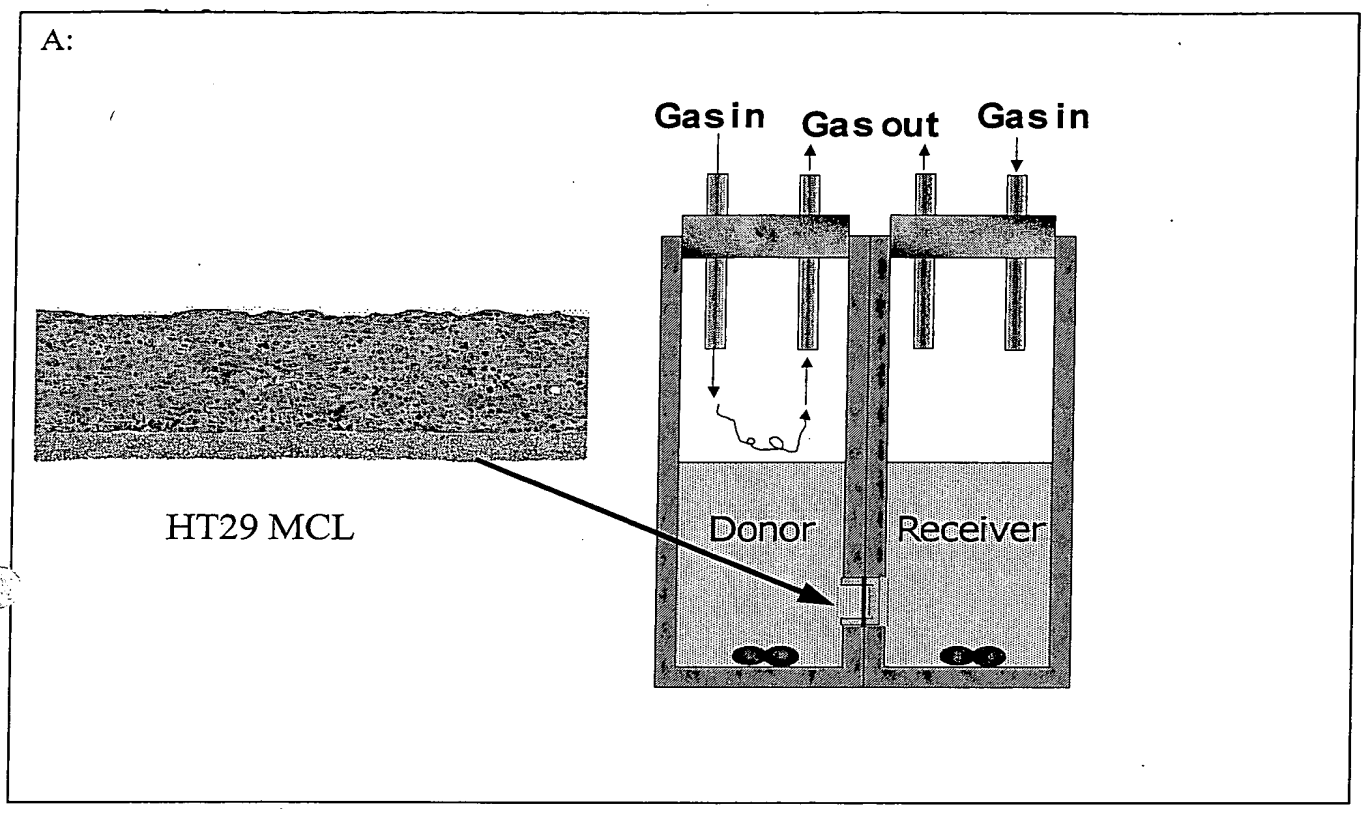
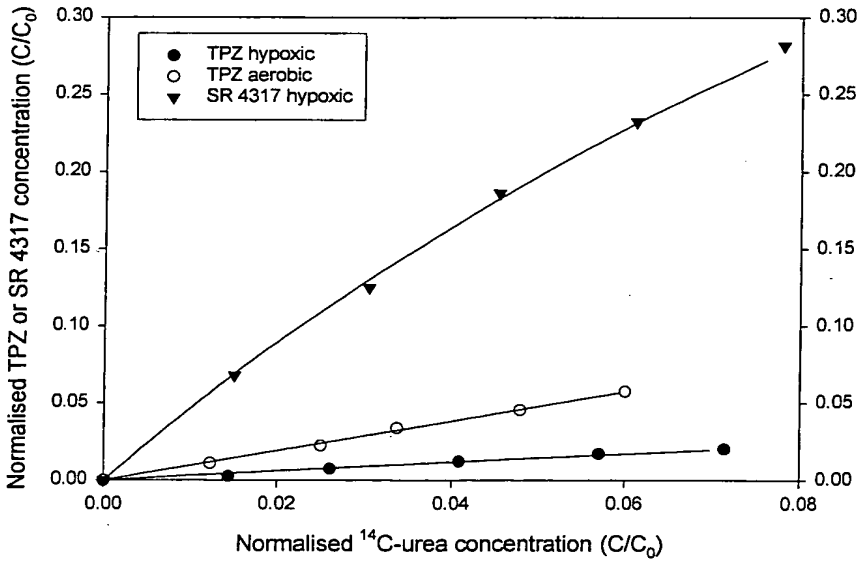

A:
Gas in
Gas out
Gas in
HT29 MCL
Donor
Receiver

Figure 5B


TPZ hypoxic
TPZ aerobic
SR 4317 hypoxic
Normalised TPZ or SR 4317 concentration (C/C0)
Normalised 14C-urea concentration (C/C0)
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0.10
0.15
0.20
0.25
0.30
0.02
0.04
0.06
0.08

Figure 6

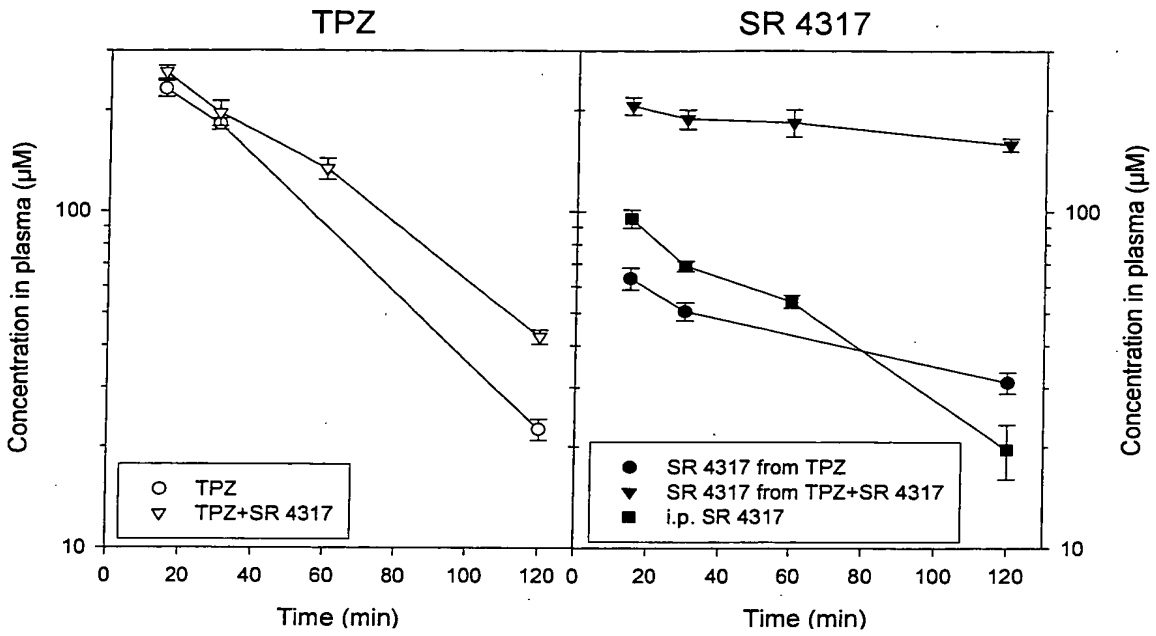
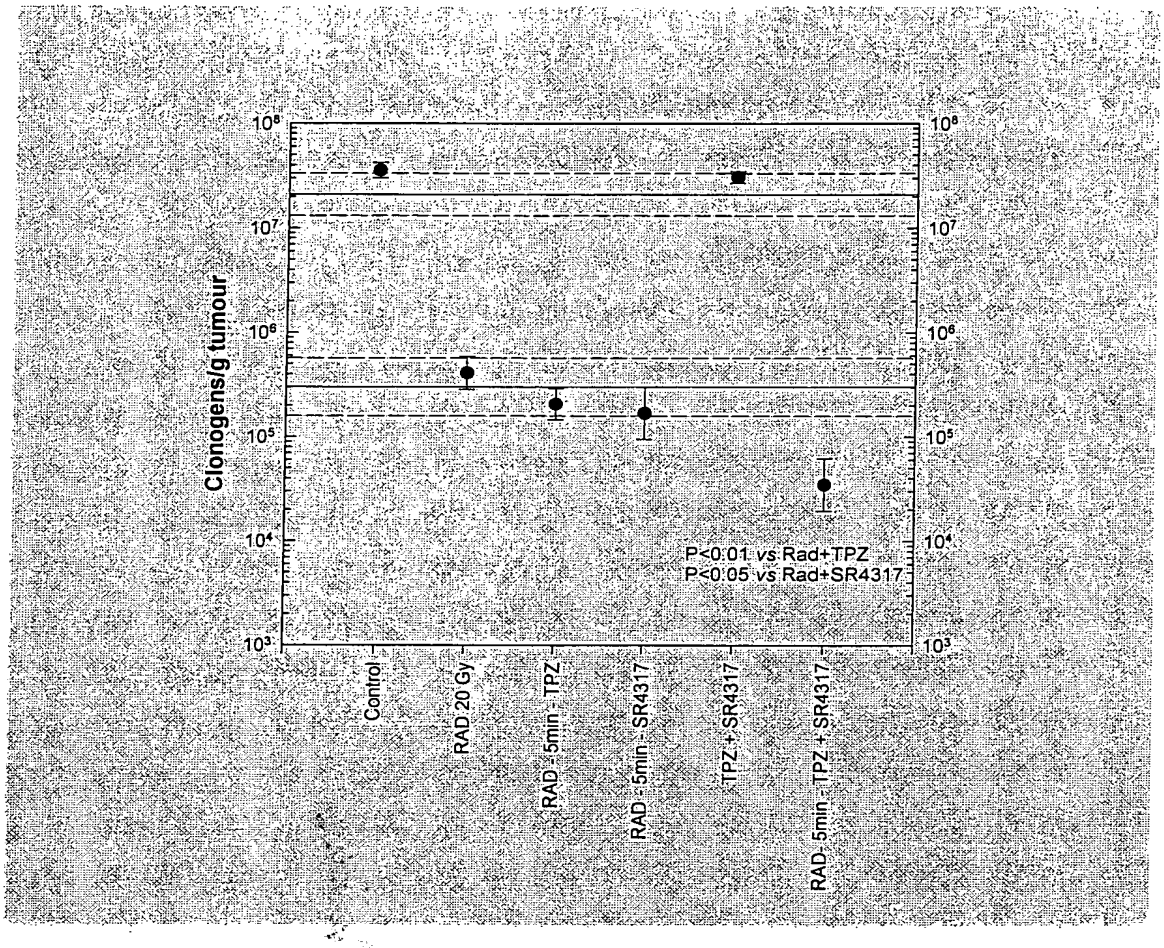

TPZ
SR 4317
Concentration in plasma (µM)
100
10
0
20
40
60
80
100
120
Time (min)
TPZ
TPZ+SR 4317
SR 4317 from TPZ
SR 4317 from TPZ+SR 4317
i.p. SR 4317

Figure 7


Clonogens/g tumour
10^8
10^7
10^6
10^5
10^4
10^3
P<0.01 vs Rad+TPZ
P<0.05 vs Rad+SR4317
Control
RAD 20 Gy
RAD -5min - TPZ
RAD -5min - SR4317
TPZ + SR4317
RAD -5min - TPZ + SR4317

5